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ORAL SURGERY
ORAL MEDICINE
and ORAL PATHOLOGY

EDITORIAL

The Second Decade of Oral Surgery, Oral Medicine, and Oral Pathology

For ten years the JOURNAL has attempted to serve its subscribers by presenting papers of interest in various branches of dentistry and allied fields. In the initial issue we forecast an enlargement of the horizon of our profession, and the horizon predicted for ORAL SURGERY, ORAL MEDICINE, AND ORAL PATHOLOGY has become more clear.

We shall continue to publish material that will widen the knowledge of our readers. There will be papers dealing with medicodental problems and unusual local diseases of the teeth, the oral mucosa, and the jaws. New techniques developed in our country and abroad will be featured. Articles of interest to both the general practitioner and the oral specialist will be included in all departments.

The *oral surgery* department will contain not only papers dealing with major oral surgery but also articles on *exodontia,* describing unusual conditions and the care of complications which may confront the dentist in everyday practice.

Oral medicine is an important department. It covers conditions that often are not only persistent and of chronic character but are also in many cases resisting the usual therapeutic efforts. Here is an excellent opportunity to compare one's own results with those suggested by authors who are able to report the results of treatment in large series of cases.

Pathology is the queen of the medical sciences and oral pathology is the foundation upon which all our diagnostic procedures are based. By investigating the histologic alterations we can understand better the clinical signs and symptoms which the patient presents, as well as the roentgenographic appearance of the diseases which affect the jaws and teeth.

Periodontia has become an important specialty, whether it is practiced by the specialist or by the general practitioner. The latter, unfortunately, even today does not always take the interest that he should in a disease which causes so many casualties in the masticatory apparatus of his patients.

We publish constantly papers by experts dealing with surgical as well as dental and medicinal procedures. The experiences of the authors should be of great value to our readers.

Endodontics is a young branch of dentistry but, alas, so all-important for the preservation of the full complement of the patient's teeth. Here many new developments occur constantly and are faithfully reported by well-trained experts who have selected this JOURNAL in which to publicize their findings.

Oral roentgenology plays an important part in the diagnosis of diseases of not only the teeth and bone but also the soft organs adjacent to them. By the aid of the injection of contrast media, we produce the sialograph, the arthrograph, and the arterio- and venograph. While not routinely used, these roentgenographic aids may have value in the diagnosis of unusual cases. In this department many practical papers will appear.

Oral anatomy, which is another department of the JOURNAL has recently been neglected. Anatomy at one time was the most important basic science for the preparation of the surgeon; today it is overshadowed by pathology. While it is often looked upon as a static science, variants from the normal occur and are worthy of consideration in diagnosis and surgical interventions. *Physiologic anatomy* still brings forth interesting findings which are of great practical value.

Anesthesiology is included, not only because of its importance to the surgeon, but also because we may point with pride to this specialty which was discovered by two dentists, Drs. Morton and Wells. These pioneers have had the vision and courage to give to the world humane methods which, after further development, have made it possible to use surgical techniques that continue to astonish the world. We hope to enlarge this department and bring to the reader all the new improvements in office as well as hospital anesthesia.

Pharmacology is another dynamic department. Not one week passes without the announcement of an important new drug. The detail man who visits our offices and our hospitals supplies literature and samples of sedatives, hypnotics, narcotics, chemotherapeutics, antibiotics, antihistaminics, antiseptics, hemostatics, blocking agents, stimulants, hormones, vitamins, and therapeutic foods. Are they safe? What side effects may be encountered? Can they be administered at the office? Should they be used only for hospitalized patients? How should they be administered—by mouth, by intramuscular injections, or by intravenous injection? What is the dose in each case?

No progress is possible without *research.* The Federal Government has approved a budget which includes $6,543,000.00 for dental health and research activities, including grants to dental schools and other research centers. The results of some of these investigations are presented to our readers.

The JOURNAL has set out to furnish the older practitioner with information of new developments in the basic sciences and contemporary techniques in oral therapy. Progress that has been made in the various special fields of endeavor has been included. The results obtained by research were featured. While the younger graduate may have obtained a broader foundation in basic medicine in dental school or has received a fuller education by taking graduate training, he still must remember that progress will continue and that it is his duty to keep abreast of developments for the sake of his patients and the health of the public.

K. H. T.

OPERATIVE ORAL SURGERY

PERSONALITY CHARACTERISTICS OF PATIENTS TREATED IN A VETERANS ADMINISTRATION HOSPITAL FOR FRACTURES OF THE MAXILLA AND MANDIBLE

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THE oral surgeon who is called upon to treat large numbers of fracture cases often finds that his work is complicated as much by the personality of the patient as by any other factor. The cooperation of these patients is often difficult to obtain, especially when the treatment is of relatively long duration. Many papers have been published in the medical literature regarding the relationship between personality characteristics and disease or injury. These studies have been applied to fracture patients by Dunbar[1] and others. Dunbar states that fracture patients as a group do not represent particularly "normal" persons.

This review was made at the Veterans Administration Hospital in Houston, Texas, to obtain information about the personality characteristics of patients who had received fractures of the maxilla and/or mandible and who had come under the care of the oral surgeons in this large hospital. All cases of fractures of the maxilla and/or mandible treated by the dental service during the period from July, 1949, through July, 1956, were studied. There were thus obtained 247 case histories that contained sufficient data to be of value. These records were carefully examined in detail to obtain any information that they might contain indicative of the cause of the fracture, condition of the patient at that time, and the degree of cooperation exhibited by the patient with his treatment. Information that could be elicited from previous hospitalization, previous diagnosis, and actions on the ward that would give an insight into the character, age, sex, employment, and compensation status of the patient were also compiled. The cases used were approximately equally distributed over a seven-year period and received treatment from a number of oral surgeons, both staff and consulting.

The oral surgeon working in a Veterans Administration hospital has an unusual opportunity to obtain information regarding the background of his

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patients. A complete medical history and physical examination by a physician are obtained on each patient treated in these installations, and information regarding previous medical treatment in the Armed Forces, compensation information, Social Service investigations, and other data are made available as required.

The largest group of patients studied was between the ages of 21 and 30 years; there were 114 cases in this class (Fig. 1). The next largest was the group between 31 and 40 years of age, in which there were 72 patients. The smallest group consisted of thirty-seven patients from 41 to 50 years of age. The patients were classified according to race and the distribution was found to be 79 per cent white and 21 per cent Negro, which is approximately the same relative racial ratio as is found in all patients admitted to this hospital. All but two of the patients studied were men, which is about the same sex ratio as for patients admitted for all causes to this hospital for the same period. The occupations of the patients were divided into skilled labor, 155 cases; common labor, 44 cases; active military personnel, 16 cases; unemployed persons, 11 cases; students, 9 cases; salesmen and clerks, 5 cases; professional persons, 4 cases; and retired persons, 3 cases. The skilled labor group represented about thirty different classifications, with the largest numbers of patients being found among truck drivers, farmers, painters, carpenters, mechanics, and longshoremen.

The cause of the fracture (Fig. 1) was found to be associated with an automobile accident in forty-one per cent of the cases, fighting in 33 per cent, falls in 9 per cent, and the remainder of the fractures resulted from assaults incident to robberies, accidents at work, gunshot wounds, and other miscellaneous causes. These figures are in sharp contrast with the usual cause of accidents, in which falls play a more prominent part.

The type of discharge from the hospital is to some extent, an indication of the cooperation of the patient. The disposition of these cases reveals that 81 per cent of the patients were discharged as having received maximum benefits from hospitalization (Fig. 2), while seventeen per cent were discharged as absent without leave from the hospital. This figure of 17 per cent "absent without leave" is contrasted with the average 2 per cent rate for this type of discharge among all patients in this hospital for all causes. However, the number of patients with fractures of the maxilla and mandible who leave the hospital "against medical advice" was significantly lower than for this type of discharge among all other patients.

The records revealed that 56 per cent of the patients studied cooperated well with their treatment, 22 per cent cooperated poorly, and 22 per cent were definitely uncooperative. Thirty-three per cent of the records studied indicated that the patient was under the influence of alcohol at the time he received the trauma that resulted in the fracture. Of the patients studied, 16 per cent were found to have received a definite diagnosis of psychiatric disease at some time. These diagnoses were distributed among nine types, with anxiety reaction, emotional instability, inadequate personality, schizophrenia, and psychotic reaction being the more common types.

From the standpoint of the oral surgeon, the patients may be grouped into three large divisions: In the first group were the patients who exhibited aggressive, belligerent, impatient, emotionally unstable, immature personality

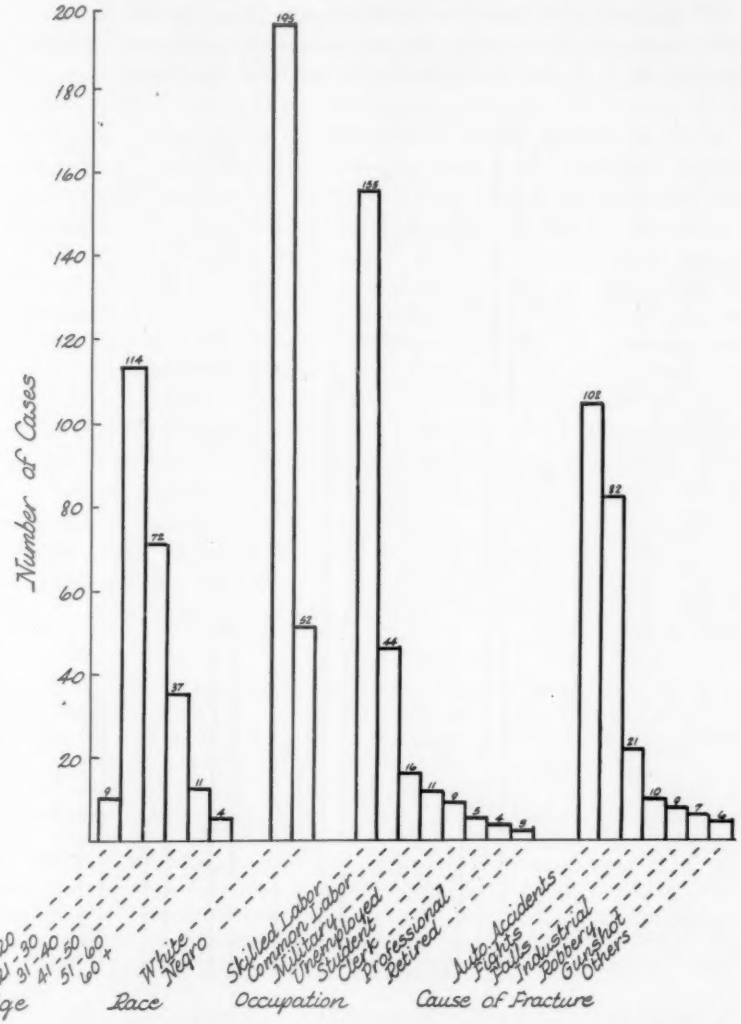

Fig. 1.—Classification of 247 cases of maxillary and/or mandibular fracture according to age, race, occupation, and cause of fracture.

characteristics. These patients generally received their trauma during fighting, and they gave considerable trouble in the hospital; 40 per cent were of this type. The patient in the second group was typically intoxicated at the time of receiving the trauma and gave difficulty in treatment during the first

few hours or days of hospital treatment but subsequently gave little or no further trouble; 29 per cent were of this type. A third group included patients who were the apparently innocent victims of an accident or assault and who gave very good cooperation with the treatment during their hospital stay; 31 per cent were classified in this group. The fact that a person had a definite psychotic background was not necessarily indicative that he would be uncooperative or that he would fail to complete his treatment.

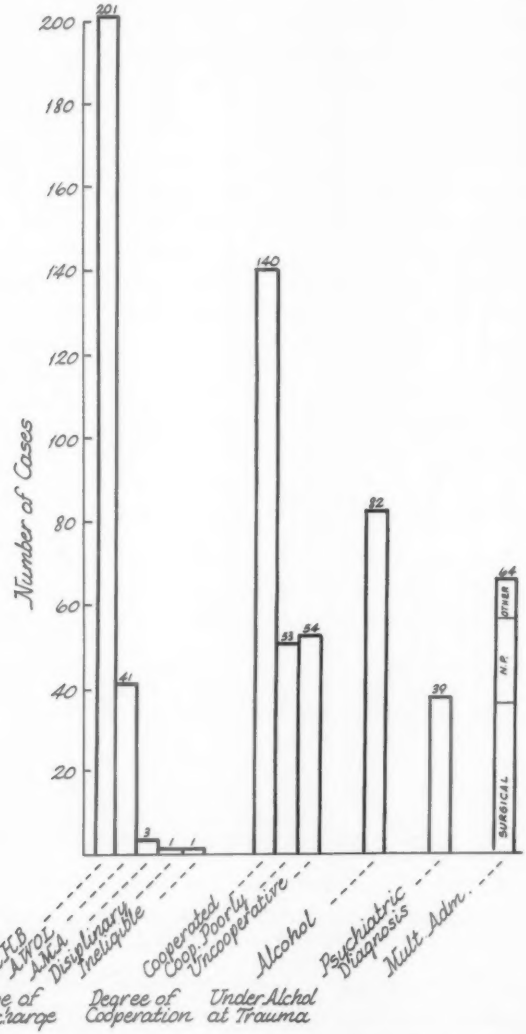

Fig. 2.—Classification of 247 cases of maxillary and/or mandibular fracture according to type of discharge, cooperation, alcohol influence at trauma, and previous psychiatric diagnosis.

The typical uncooperative or poorly cooperative fracture patient had certain personality characteristics that are noted again and again in the histories of these persons. Some of these characteristics are impatience, rebelliousness, aggressiveness, suspicion of all those around them, a demanding attitude, impulsiveness, and belligerence. They tended to be emotionally immature, unstable, and unable to fully control their temper. They made many demands upon the surgeon for more and more sedation and attention. In many cases their families were also the cause of trouble on the wards due to their demands and impatience. These patients were found to have a history of having had numerous jobs of relatively short duration, and many notations of broken homes and multiple divorces are found in the available social histories. Treatment was often made more difficult by their delay in seeking care after the fracture was obtained. Five per cent of all the patients studied had been treated for two or more fractures of the maxilla or mandible. In several cases, additional fractures were received while the patient was on leave from treatment for the one that originally brought him to the hospital. Twenty-six per cent of the patients studied had multiple admissions to the hospital. These admissions were as follows: 56 per cent for surgical treatment, 29 per cent for neuropsychiatric treatment, and 15 per cent for all other types of treatment.

The length of stay as an inpatient was tabulated and found to be twenty-two days for patients treated only for fracture of the maxilla and/or mandible. The most prominent factor that led to a long hospitalization was found to be delay in reporting for treatment with the result that osteomyelitis had developed, which greatly complicated the treatment of the patient's fracture.

Typical case histories are given to illustrate the various types of patients treated.

Case 16 was that of a 30-year-old white male longshoreman who gave a history of daily alcohol intake; he was in an alcoholic stupor upon admission. He had received a fracture of the maxilla as a result of a fight. After this patient was aroused from his stupor, he gave no difficulty on the ward and cooperated fully with his treatment.

Case 20 was that of a 35-year-old unemployed white man who was receiving a 30 per cent compensation for neuropsychiatric disease. This man received a bilateral fracture of the condyle necks of the mandible as a result of an auto accident. He became so violent after admission that he had to be transferred to a closed ward on the neuropsychiatric service. He was emotionally unstable with rapid changes in mood. He had difficulty in his naval service even though he served fifty-six months. His difficulties continued in civilian life and were marked by chronic alcoholism. The history revealed several absences without leave from other hospitals. This patient cooperated poorly, but completed his treatment for the fractures.

Case 23 was that of a white male welder, 39 years old, who received a fracture of the mandible as a result of a fist fight while intoxicated. He had previously been diagnosed as a psychoneurotic of the hysterical type. His chart revealed histories of several other fractures and a gunshot wound. He failed to complete his treatment when he left the hospital without permission and never returned.

Case 33 was that of a 26-year-old white male student who stated that he was injured as a result of a fight with three other men. He failed to complete his treatment by not returning to the hospital after he was given a pass. His mandibular fracture, which he

received in 1951, was the fourth injury he had received in night club brawls. He had received a severe laceration in 1946, a gunshot wound in 1949, and a serious stab wound in 1950.

Case 65 was that of a 32-year-old white male longshoreman who was involved in an altercation and received a fracture of the mandible when he was struck with a handle of an auto jack. Treatment was completed in approximately one month, and about a month later he received a fresh fracture of the mandible as a result of a blow from a fist. The patient gave trouble on the ward by leaving the hospital for the purpose of obtaining alcohol. He failed to complete the treatment for the second fracture.

Case 75 was that of a 47-year-old white man, a common laborer, who was admitted for fracture of the mandible as a result of a fist fight. This patient had a long history of admissions to VA hospitals because of an inadequate personality and paranoid ideas. He had a very poor work record and was unable to meet the requirements of every-day living. He completed his treatment for fracture without difficulty.

Case 76 was that of a 23-year-old white unemployed man who stated that he was standing on a street corner when he was sat upon by a number of men and beaten with a piece of pipe as he was "strictly tending his own business." This patient's history reveals a very unhappy childhood. He was an orphan who was adopted at an early age. He had a number of discharges from the Armed Services for unsatisfactory service since first enlisting at an early age. This patient committed no overt acts in the hospital, but gave continued difficulty on the ward by his passive resistance. After a long stay in the hospital, his treatments were finally completed.

Case 116 was that of a 34-year-old white man, an electronic technician, who received a fracture of the mandible when his car ran into an open ditch. He stated that he had been involved in an argument with some of his fellow workers. Immediately afterward he got into his car and drove at a high rate of speed, running his car into a ditch when he lost control. Despite the fact that this patient was an immature personality, he completed his treatment without difficulty.

Case 138 involved a 22-year-old Negro man, a common laborer, who received a bilateral fracture of the mandibular condyle as a result of a fall during an epileptic attack. This patient was a troublemaker on the ward, who attempted to start fights with his fellow patients. He failed to cooperate with his treatment and removed his appliances. He was retained in the hospital and in this way his treatment was finally completed.

Case 193 was that of a 23-year-old white male printer who received a fracture of the maxilla as a result of an automobile accident. This patient was a schizophrenic who was unable to integrate with other people. He had many neuropsychiatric admissions. Despite the fact that he acted aloof, superior, and arrogant while in the hospital, he carried through with a relatively long seventy-nine day treatment period.

Case 205 was that of a 45-year-old white man, a common laborer, with a previous diagnosis of schizophrenic reaction and a service-connected disability discharge for inadequate personality. This patient cooperated with his treatment, but it was most difficult to get him out of the hospital, as he quickly became "institutionalized" and wanted to remain.

Case 231 was that of a 56-year-old white farmer who had a history of difficulty since a very early age. During a paranoic hallucination he ran from his house with a shotgun in his hand and received a gunshot wound in the right mandible, possibly as the result of a fall. This patient gave no difficulty whatsoever after the first week in the hospital and cooperated well with the extensive work necessary to rebuild his face.

Case 239 was that of a 34-year-old Negro male cook who had satisfactorily served 36 months in the Service. He received a fracture of the mandible as a result of a fight. This patient revealed an excitable, impulsive, and unstable personality with chronic maladjustment, and he was given a disciplinary discharge from the hospital for drunkenness and fighting on the ward.

SUMMARY

The case histories of 247 patients admitted to the Veterans Administration Hospital in Houston, Texas, for treatment of fractures of the mandible and/or maxilla were studied. Information regarding the cause of the fractures and personality characteristics of the patients was obtained. This material was tabulated to reveal the personality types of these patients.

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ACUTE OSTEOMYELITIS OF THE MAXILLA

Report of a Case

Raymond J. Englert, D.D.S., and Harry N. Pasqual, D.D.S., Pittsburgh, Pa.

OSTEOMYELITIS may occur in acute, subacute, or chronic form, and it may involve either a widespread area or a small localized section of bone.

The case to be described involved the alveolar process of the maxilla, which was locally traumatized by a laryngoscope during an attempt to pass an endotracheal tube for surgery under general anesthesia.

The patient's general systemic condition was very poor, and her resistance to infection was low. Thoma[7] also states that there is a correlation between local trauma and low resistance to infection.

CASE REPORT

History.—M. U., a 51-year-old white woman, was admitted to the hospital on Dec. 8, 1956, with acute abdominal pain. Physical examination revealed a well-developed, well-nourished white woman with extreme tenderness of the upper right quadrant of the abdomen. Oral examination revealed a completely edentulous mouth. All other physical findings were normal. All blood and urine tests were within normal limits. Roentgenograms revealed the presence of numerous stones within the gallbladder and duct. The case was then diagnosed as chronic cholecystitis and cholelithiasis.

On Dec. 17, 1956, the patient was prepared for surgery. Following induction of endotracheal anesthesia, a cholecystectomy and exploration of the common duct were performed. The patient was returned to her room in satisfactory condition.

The postoperative period, however, was marked with severe pain and frequent periods of vomiting. Postoperative roentgenograms revealed the presence of a stone in the common duct. It was then evident that more surgery was indicated. On Jan. 7, 1957, the patient was returned to the operating room for removal of a cholelithiasis. While an attempt was being made to pass an endotracheal tube with the aid of a laryngoscope, the mucous membrane of the anterior maxilla was lacerated. The tube was then passed and surgery was completed following the removal of two more stones from the common duct.

The postoperative period was again complicated by the development of a pancreatitis and a marked fluid balance disturbance. A complete blood count on Jan. 12, 1957, revealed: hemoglobin, 8.5 grams or 55.1 per cent; color index, 0.95; erythrocytes, 2,940,000; leukocytes, 36,550; polymorphonuclear leukocytes, 93 per cent; and lymphocytes, 6 per cent.

The patient had received whole-blood transfusions and daily antibiotic therapy; her intake and output had been kept under close surveillance. She appeared very weak, and her pulse was very thready. Prognosis at this time was considered poor.

A follow-up blood count revealed an increase in both erythrocytes and leukocytes. Recovery was slow and marked with numerous complications. On March 12, 1957, a dental consultation was requested because of the development of an oral lesion.

Intraoral examination revealed a completely edentulous mouth. There was a large, deep laceration or ulceration of the right maxilla in the muscle fold under the lip. The bone was quite denuded, and the surrounding tissue was extensively ulcerated. The tentative diagnosis was that of a "traumatic ulcer" or "malignancy."

Roentgenographic examination showed the presence of a small osteolytic process in the anterior region of the maxilla.

Biopsy.—Bone and tissue removed from the right maxilla presented the appearance of osteomyelitis rather than a malignancy. A large area of bone which looked as if it would sequestrate was loose. The specimen was sent to the laboratory for routine microscopic examination.

Fig. 1.—Appearance of sequestrum prior to removal.

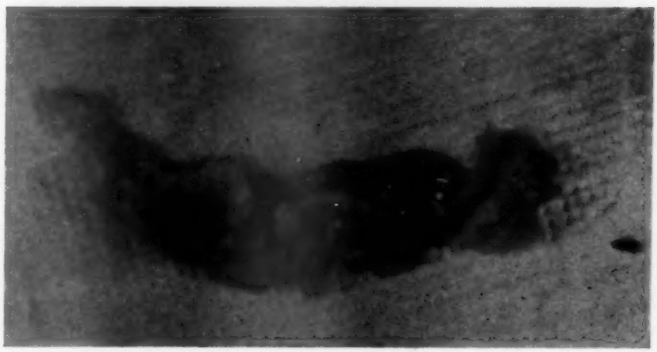

Fig. 2.—Sequestrum specimen.

Histopathologic Report.—There were several small fragments of bone and necrotic tissue from the right maxilla 0.5 cm. in size. Portions of bone were partially covered by squamous epithelium. Beneath this could be noted necrotic bone tissue, throughout which were scattered many chronic inflammatory cells. The lacunae of the bone were empty. Scattered throughout were noted foci of neutrophils.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 3.—Immediate appearance following sequestrectomy.
Fig. 4.—One month after sequestrectomy.
Fig. 5.—Complete healing of maxilla two months following sequestrectomy.

Diagnosis.—Acute osteomyelitis.

It was decided at this time not to interfere surgically with the osteolytic process. The patient was discharged from the hospital and was seen at least once a week at her home, where she was confined to bed. She was receiving adequate antibiotic therapy, bed rest, and nursing care. Six weeks following her discharge from the hospital, we decided to remove the sequestrum. Without the aid of any anesthetic, but adhering to a strict sterile technique, we applied an Allis forceps to the dead bone and, without pressure, gently lifted the sequestrum from the maxilla. All of the sequestrum was removed and the area was explored with a curette for any remaining loose fragments or spicules of bony tissue. Bleeding was minimal. The entire procedure was performed with the complete absence of pain.

One month following the removal of the necrotic bony tissue healing was evident and the patient's general systemic condition was markedly improved.

Four months after the patient's hospital discharge, healing was complete and she voiced the desire to have new dentures made.

DISCUSSION

There is no question that trauma and low resistance to infection were the causative factors in this case. Because of the complete coverage with antibiotics and the patient's grave postoperative period, it was decided not to interfere surgically but to allow the osteoclasts to separate the dead bone sequestrum from the living; this, of course, facilitated the removal of the sequestrum.

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PROTEOLYTIC ENZYMES (INTRAMUSCULAR AND TOPICAL)—AN AID IN TREATMENT OF REFRACTORY DRY SOCKETS (LOCALIZED ACUTE ALVEOLAR OSTEOMYELITIS)

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ONE of the most distressing of all postoperative sequelae to tooth removal is the so-called "dry socket." The term "dry socket" is a misnomer, but it has become accepted by common usage. Other common names for this condition are alveolitis, localized osteomyelitis, alveolar osteitis, postoperative osteitis, postextraction alveoalgia, and others. I prefer the term "localized acute alveolar osteomyelitis." By whatever name it is called, the condition is characterized by excessive, excruciating pain of long duration, starting as early as the first day after extraction and as late as the seventh day,[1] and lasting as long as forty days.[2]

The condition is relatively uncommon. Archer[1] reports 226 cases out of 24,575 extractions, approximately 0.9 per cent. Krogh[3] reports an incidence of 2.17 per cent, and others[1] report an incidence of as much as 3 or 4 per cent. All agree that the condition occurs about twenty times more frequently in the mandible than in the maxilla.[2] Cahn[4] states: "The blood supply of the area is the determining factor. In the maxilla there is a profuse blood supply and much collateral circulation; the bone does not depend on a main nutrient vessel. In the mandible the blood supply is dependent chiefly on one vessel, the inferior dental artery." In Archer's[1] report, 62 per cent occurred after extraction of vital teeth, while Zimmer[5] found occurrence in the ratio of three nonvital teeth to one vital tooth.

The etiology is unknown, and localized acute alveolar osteomyelitis occurs in spite of the most exacting operative technique and the most careful aseptic procedure and regardless of the ability and judgment of the operator.[2] Many theories have been advanced as to its cause: pre-existing infection, trauma to the bone during extraction, decreased bleeding due to epinephrine in the local anesthetic, infection entering after tooth removal, loss of clot because of rinsing or sucking the wound, dietary deficiences,[6] traumatic occlusion, curettement after extraction, and poor physical condition of the patient.

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Thoma[2] states: "Inadequate blood circulation in the alveolus and perhaps a pre-existing infection in the lamina dura of the alveolar socket originating from the tooth infection are the best explanations." Cahn[4] states: "The direct cause of osteomyelitis is infection. Also trauma imposed on an already overburdened tissue usually results in the more serious lesion."

A brief review of the steps in normal healing of a socket after extraction can be summarized, according to Weinmann and Sicher,[7] as follows:

1. Formation of a blood clot filling the socket.
2. Organization of the blood clot by proliferative young connective tissue.
3. Gradual replacement of the young connective tissue by coarse fibrillar bone.
4. Reconstruction of this region of the alveolar process by resorption activity on the one side and replacement of the immature bone by mature bone on the other.
5. Epithelization and healing of the surface wound occurs simultaneously with the other reparative processes.

Failure of formation or the early removal of the blood clot leads to complications in the healing of the socket. Areas of the denuded alveolar bone necrotize, by reason of infection, and are slowly eliminated by undermining resorption. This condition of the alveolar bone suggests localized inflammation. The filling of the socket takes a long time, since the proliferative granulation tissue is exposed to insults of chemical, mechanical, and bacterial nature; development is thus retarded. The patient invariably complains of an extremely fetid taste. Pain is severe and frequently is felt in the region of the ear as well as in the socket. It is a radiating type of pain and is often described as a throbbing or pounding sensation. Inspection discloses that the blood clot is either entirely spent or badly broken down, soft and mushy, and necrotic, with a dirty grayish cast. A blunt flexible probe will meet with little or no resistance and will cause increased pain if allowed to touch the socket wall.

Since the alveolar bone is able to give only a rather feeble defense against infection, logically because it is not as vascular as soft tissue, necrosis occurs. Elimination of this dead bone by resorption rather than by osteoclastic activity or sequestration takes a long time. It is with these refractory cases of dry socket that this investigation is concerned. The purpose of the investigation was to find a more satisfactory and quicker method than that presently known for safe removal of the necrotic clot and bone. It is not the purpose of this article to review or criticize the many established methods of treating refractory dry sockets. Previous to this investigation, however, my most satisfactory results were obtained by the combined use of antibiotic therapy and Levine's[8] recommended use of a cone of zinc oxide—eugenol paste gently placed in the socket.

Since it has been established conclusively by many investigators,[9] and summarized by Olinger[10] in 1954, that proteolytic enzymes parenterally and topically have the ability to digest dead tissue and fibrin clots without adversely affecting normal tissue or normal healing processes and are specific anti-inflammatory agents,[11] the following two-year study (1955-1957) on their effectiveness in eighty-six cases of acute refractory dry sockets was initiated (Table I).

TABLE I

Mandible
Eighty-one cases (76 referred, 5 the author's)
54 third molars (vital)
30 traumatic removals
24 simple removals
10 second molars
7 vital traumatic removals
3 simple, periodontally involved, removals
12 first molars
8 vital traumatic removals
4 simple, periodontally involved, removals
5 premolars
4 nonvital traumatic removals
1 vital simple removal
Maxilla
Five cases (all referred)
4 vital cuspids, traumatic removals
1 first molar, nonvital traumatic removal

All eighty-six cases presented acute, almost unbearable pain. The average postextraction time was five days. Immediate pain control was the primary consideration in all cases. Usually it was necessary to give subcutaneous injections of Demerol, morphine sulfate, or Nisentil (alphaprodine hydrochloride) in dosages determined according to individual requirements.

TREATMENT

The treatment was divided into two phases—systemic and local.

First Visit.—Immediate relief of pain described above.

Systemic treatment included administration of antibiotics as follows: (1) Intramuscular (gluteal) injection of 600,000 units of procaine penicillin G in aqueous suspension. (2) Oral tetracyline, 500 mg. immediately and 500 mg. every four hours for four days. (If the patient had a known sensitivity to penicillin, then erythromycin, 250 mg., and tetracycline, 250 mg. orally every four hours, were given instead.)

This was followed by a deep gluteal muscle injection of 1 c.c. (5 mg.) lyophilized trypsin aqueous (Parenzyme aqueous, National Drug Company, Philadelphia, Pennsylvania). Parenzyme aqueous drastically reduces the incidence of pain and related side effects that Parenzyme suspension in sesame oil produces at the site of injection, and it has been found to be equally as effective. (Rationale: Lyophilized trypsin is a specific anti-inflammatory agent.)

In the *local* phase of treatment the socket was isolated with cotton rolls and a pledget of cotton saturated with 5 per cent Xylocaine ointment was gently teased into the socket and left for five full minutes to control local pain. This was removed and the socket was irrigated thoroughly with a solution of 125,000 Armour units of crystalline trypsin in Sorensen's phosphate-buffered solution.[10] Then a pledget of cotton saturated in the above solution was placed in the socket for fifteen minutes; this removed slough and necrotic debris. Next a cone of thick zinc oxide-eugenol paste, slightly smaller than the socket, was gently teased into the socket. The patient was then dismissed until the next day.

Second Visit.—In seventy-four cases, patients returned completely asymptomatic. All received another 5 mg. injection of lyophilized trypsin. Oral antibiotic therapy continued for an average of five days. The zinc oxide-eugenol cone was left in until exfoliated, usually within five days, and patients were dismissed.

In four cases patients experienced reduced pain. Local treatment was repeated, and on the third day the patients were asymptomatic.

In three cases local treatment had to be repeated for four continuous days, and eventually a large sequestrum of bone was exfoliated.

DISCUSSION AND SUMMARY

In a two-year study of eighty-six cases evidence has been presented of the effectiveness of proteolytic enzymes in reducing the healing time of refractory acute alveolar osteomyelitis.

I am conducting studies, with very favorable results to date, on its effectiveness in the treatment of pericoronitis, cellulitis, acute alveolar abscess, and acute maxillary sinusitis in conjunction with repair of oroantral fistulas; as preventive anti-inflammatory therapy for multiple extractions, impactions, alveolectomy, and apicoectomy; as a therapeutic measure after reduction of fractures; in hastening the absorption of edema and hematomas; and in temporomandibular joint disturbances caused by inflammation.

Proteolytic enzymes have been found to have no contraindications. They have no systemic side effects, and they do not interfere with the blood-clotting mechanism. They do not spread or mask infection; nor are they incompatible with antibiotics or other drugs.

I feel that proteolytic enzymes are a valuable adjunct in oral surgery, and I encourage further investigations.

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IRRIGATION OF THE MAXILLARY ANTRUM USING AN INTRAORAL ROUTE

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IN CASES referred to the oral surgery unit of a hospital antral lavage is sometimes needed, either as a diagnostic aid or for treatment, and the procedure can be carried out very easily through an intraoral approach.

Irrigation of the maxillary antrum through the mouth is not new. Fickling,[1] in the introduction of a paper, calls attention to Cowper's operation in which an upper molar tooth is removed and a hole is made through the alveolus to gain access to the sinus. Later he quotes Charles Tomes: "When there are no diseased teeth a sound first molar may be extracted, or the puncture made near the malar process, or backwards from the canine fossa. . . ." Again I quote from Fickling's paper: "Gradually the disadvantage of Cowper's operation became apparent and it was replaced by an approach through the canine fossa and later the modern intranasal antrostomy in the inferior meatus became standard practice."

The ear, nose, and throat surgeon now uses an intranasal route in which, after applying a surface anesthetic to the mucosa, he introduces a trocar and cannula into the sinus through the lateral wall of the nose in the inferior meatus. The trocar is then withdrawn and a syringe is attached to the cannula. Although this technique is straightforward enough, it was thought that it would be more acceptable to dental personnel to use a route through more familiar territory. Furthermore, good anesthesia is obtained easily and quickly by the usual submucous injection.

The instruments required are simple and consist of a dental hypodermic syringe, local anesthetic, warm saline, trocar and cannula (which should be of small gauge), record syringe to fit the cannula, and a dish to collect the return washings from the nose. A rubber connection between cannula and syringe is sometimes used to advantage to enable the syringe to be held clear of the dish. Radiographic examination of the maxillary sinuses should always be made prior to lavage.

Anesthesia is obtained by the infiltration of any suitable local anesthetic in the region of the canine fossa, that is, distal to the apex of the upper canine tooth and extending posteriorly to the first molar area. When anesthesia is obtained, the point of a trocar and cannula pierces the mucosa at a place well out

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Fig. 1.—Photograph showing point of entry of trocar and cannula. A finger should always be placed near the end of the cannula. It is omitted here for clarity.

Fig. 2.—Lateral-skull x-ray film with cannula in position.

in the sulcus distal to the canine and above the apices of the premolars (usually the second) or the mesial root of the first molar (Fig. 1) and is directed upward, backward, and slightly inward. The bone is pierced by rotating the trocar and cannula clockwise and anticlockwise and applying gentle pressure, which varies in individual cases but is never very great. The cannula is felt to slip suddenly into the antrum in much the same way as a burr is felt to enter the pulp chamber when opening it through the cingulum of an upper anterior tooth. A finger should always be placed about ½ inch from the end of the cannula to prevent its passing too far into the antrum and possibly piercing the floor of the orbit. The trocar is now removed, an empty record syringe is attached to the cannula, and the plunger is carefully withdrawn. This is done because it is important to ascertain that the end of the cannula is in the antral air space and not embedded in swollen antral mucosa. If the plunger withdraws easily and the syringe remains empty, the end of the cannula must be in the antral air space and the ostium is not blocked. If the end of the cannula is in pus, this, of course, will appear in the syringe. Usually the air space will have been entered and the syringe may then be filled with warm saline and attached to the cannula, either directly or through a flexible rubber coupling.

The patient is instructed to lean the head well forward so that the return washing, having passed through the ostium into the nose, is directed away from the nasopharynx and out through the external nares into the dish placed to receive it. Mucus or pus may be contained in the return, and this or any pus previously obtained in the syringe should be sent to the pathologic laboratory for determination of the type of organism and antibiotic sensitivity. Several syringefuls should be used, the last one being 3 per cent Argyrol or a solution of penicillin as the operator prefers. (I prefer Argyrol.)

This method has now been used on numerous cases in the last five years; no complication has arisen, and the puncture wound has healed without difficulty. The procedure is easy to perform, and there is a minimum of discomfort for the patient, provided that the head is inclined well forward to prevent the return from passing backward into the pharynx.

In cases in which the antrum has already been explored through a Caldwell-Luc approach it is, of course, not necessary to use a trocar and cannula to pierce bone, and a wide-bore hypodermic needle attached to the syringe passes through easily following anesthesia of the area. This method is also less unpleasant for the patient than lavage through an intranasal antrostomy opening.

My thanks are due Miss Perry, Medical Artist at Crumpsall Hospital, Manchester, for clinical photographs and reduction of radiographs.

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224 Dobcroft Rd., Ecclesall

SEBACEOUS CYST FROM THE FLOOR OF THE MOUTH

Report of a Case

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THE patient, a 5-year-old white American girl, was referred by her family physician for treatment of a swelling in the floor of the mouth.

CHIEF COMPLAINT

The parents stated that a hard, firm mass in the midline of the floor of the mouth had existed for about one year.

HISTORY OF PRESENT ILLNESS

The girl had had no previous hospital admission, no recent accidents, no operations, and no serious illnesses. She had received recently a series of Salk vaccine injections.

FAMILY HISTORY

Her mother and father were living and well. There was no history of cancer, lues, tuberculosis, or allergy; this child was not sensitive to any antibiotics.

CLINICAL EXAMINATION

The patient was lying quietly in bed. She was not suffering from pain, but she seemed to be somewhat handicapped in her speech. There was no adenopathy. The general condition was good. The teeth were present. The tongue was normal in size, color, and consistency; however, it appeared elevated and was definitely interfering with her eating and her speech. Close inspection revealed a hard, round mass about the size of an English walnut, definitely encapsulated and lying in the midline just below the inferior frenum and the anterior portion of the tongue. It was evidently lying above the mylohyoid muscle. There was some redness throughout the anterior floor of the mouth. This mass was readily localized as revealed by a bimanual examination.

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The impression was that the mass was a dermoid cyst or a ranula. Laboratory findings were within normal limits.

ROENTGENOLOGIC FINDINGS (DRS. A. K. BUTLER AND J. L. CURRY)

No abnormal appearances were demonstrated. The clinically evident soft tissue tumor near the midline and in the floor of the mouth was not demonstrated on multiple film views, including an intraoral occlusal film.

OPERATION

The patient was given Seconal sodium, 2 c.c., and scopolamine, 1/300 gr., one hour before the operation.

General anesthesia was induced with Pentothal sodium, 2.5 per cent, followed by nasotracheal intubation and maintained with nitrous oxide and oxygen.

Fig. 1.

By sharp and blunt dissection, the tumor mass was exposed from the midline of the floor of the mouth and beneath the tongue and also above the mylohyoid muscle. It was removed in toto. Catgut 000 was used to close the incision. The tumor mass was sent to the laboratory for microscopic examination.

Postoperatively, the patient was given penicillin, 600,000 units, once a day; ice bags for twenty-four hours; elixir phenobarbital, 1/8 gr., twice daily and at bedtime; saline mouthwash every three hours, utilizing the polyethylene feeding tube (K-30) and Sustagen as a supplement to the liquid diet.

PATHOLOGIC REPORT (H. G. LITTLE, M.D.)

Gross: The specimen consisted of a piece of tissue which measured 1.5 cm. in diameter and was pinkish in color. On sectioning, a sebaceous cyst with white waxy material was exposed.

Microscopic: Sections of the tissue showed a sebaceous cyst. Part of the wall was formed by stratified epithelium, the inner surface of which was keratinized. Part of the tumor surface was formed by granulation tissue in which there were histiocytes and giant cells of the foreign body type. The epithelium rested upon dense fibrous connective tissue in which could be seen remnants of sebaceous glands and hair follicle. In the part of the connective tissue there was a small collection of polymorphonuclears supported by granulation tissue.

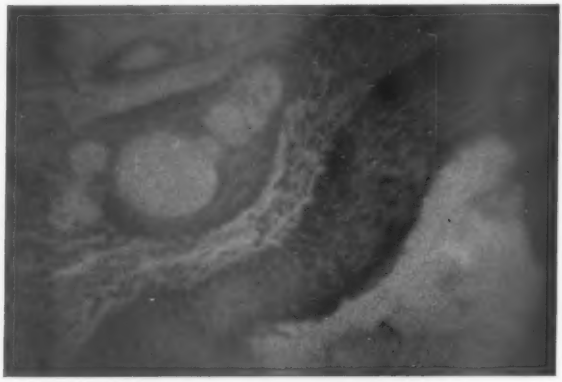

Fig. 2.

Diagnosis: Sebaceous cyst arising from aberrant sebaceous gland of the oral mucosa in the floor of the mouth.

COMMENT

Dermoid cysts may be found in the floor of the mouth above the mylohyoid muscles and between the genioglossus muscles. They may feel firm, and they may be well encapsulated. Unless the cyst is biopsied, a diagnosis is somewhat difficult.

Boyd[2] states: "Dermoid cysts are often termed sequestration dermoids because they are formed by the inclusion of the skin during the closure of one of the various embryonic clefts and fissures. The cysts consist of a fibrous wall of true skin (cutis vera) lined with stratified epidermis, showing the normal papillary arrangement and containing hair follicles, sweat glands and sebaceous glands." He further states that "a sebaceous cyst forms as a result of an obstruction to the duct of a sebaceous gland."

Therefore, there should be no doubt that epidermal inclusions are embryonic cells. These cells in the early years are dormant. Later, they grow into their mature forms and develop into teeth, sebaceous glands, sweat glands, mucous glands, and hair as the case may be. We believe that it is after the full development of these glands and tissues has occurred that a cyst may form. The combination of these fully developed glands and tissues results in a bulky mass which later becomes cystic. An occurrence of this type is a dermoid cyst.

On the other hand, although a hair follicle and aberrant sebaceous glands were found in this particular case, we have a strong belief that the formation of this cyst was due only to the accumulation of sebaceous matter as a result of the obstruction of the ducts of the sebaceous glands. Because of the abnormal location of these glands (sebaceous), it is impossible for them to secrete their products to the external surface. Therefore, the secretions are accumulated, resulting in an encapsulated soft mass. Anderson[1] states: "Sebaceous cysts may occur on a dysontogenetic basis or may follow occlusion of the gland."

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EXODONTIA

DENTAL HEMORRHAGE

Lawrence Cohen, B.Ch.D., F.D.S.R.C.S.(Eng.), L.R.C.P., M.R.C.S., London, England

THERE are many articles in the literature relating to dental hemorrhage. Many of these articles list numerous drugs and other methods for stopping hemorrhage following tooth extraction. One feels that the authors cannot possibly use the multiplicity of methods and materials which they describe, for they fail to mention their own experiences. It is the purpose of this article to mention only those methods for the arrest of dental hemorrhage which have proved to be of value in my own experience.

Not all patients who bleed excessively following tooth extraction have a blood dyscrasia. Many of the patients who present with dental hemorrhage have had extractions in the past and have not bled excessively. When profuse hemorrhage occurs after tooth extraction in a healthy patient, the bleeding probably results from fractures of the alveolus or laceration of a large vessel in the soft tissue. In the majority of cases, suturing of the socket with 00 black silk after débridement of loose portions of alveolus is sufficient to arrest the hemorrhage. The patient is then instructed to bite on a gauze pad for ten minutes. I have had little success with packing gelatin sponge or the commercial alginate preparations into the socket in the treatment of dental hemorrhage. When these have been employed together with suturing of the socket, the hemorrhage has stopped and one wonders whether this was because of the suturing.

In my opinion, the astringents have no place in the control of dental hemorrhage. Viper venom has been found to be of little value.

In hospital practice one is often called upon to extract teeth for patients with severe toothache who have such blood dyscrasias as hemophilia, Christmas disease, and leukemia. When it is known that the patient has a bleeding tendency, this should be thoroughly investigated before tooth extraction.

From the Dental Department of Middlesex Hospital.

Fig. 1.—Dental plate to prevent postoperative hemorrhage.

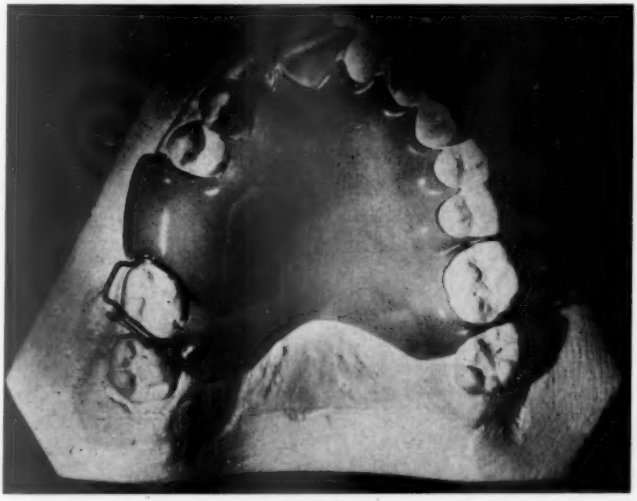

Fig. 2.—Plate on model. Tooth to be extracted has been cut off the model.

MANAGEMENT OF HEMOPHILIACS UNDERGOING TOOTH EXTRACTION

Hemophilia, a congenital hemorrhagic disease occurring in the male, is due to deficiency in the blood plasma of antihemophilic globulin (α-prothromboplastin). Christmas disease is due to a deficiency of Christmas factor (β-prothromboplastin).

Some hemophiliacs have a mild form of the disease and do not bleed excessively following tooth extraction. The hemophilic patient should be hospitalized for extraction of teeth. Before operation, which is always performed under general anesthesia, the patient is transfused with fresh whole blood or plasma. A dental plate is constructed preoperatively to control the hemorrhage (Fig. 1). Impressions are taken of the upper or lower jaw, depending upon the site of the proposed extraction. A model is cast in stone, and the tooth to be extracted is cut off the model. This part of the model is then covered with a layer of tin foil. Adams' cribs are used for the retention of the appliance. If the first molars are present, cribs are placed around them. When these teeth are missing, the second molars or premolars can be used for retention. A plate is then constructed of acrylic resin (Fig. 2). Following extraction of the tooth, the plate is inserted with a little zinc oxide and eugenol over the site of extraction. This plate may be left in situ for two to three weeks without removal. The patient can eat and drink quite normally, and it is found that the plate prevents postoperative hemorrhage.

In patients with Christmas disease who require dental extractions, a similar procedure is employed, except that stored blood or serum can be transfused instead of the fresh blood or plasma necessary in hemophiliacs.

In treating a patient with a blood dyscrasia one should extract only those teeth which it is absolutely necessary to remove. Medical opinion should always be sought on the advisability of extraction. In cases of acute leukemia, extractions should be avoided. I have extracted teeth, with no untoward effects, for patients with chronic leukemia when the disease was under control by the physician. In these cases preoperative blood transfusion was given. In the case of those patients with a blood dyscrasia who have pain and for whom extraction is not advisable, the pain should be relieved with analgesics and with obtundent dressings.

SUMMARY

For postoperative hemorrhage, suturing of the socket is advised. An artificial denture for the prevention of hemorrhage following tooth extraction is described. The importance of seeking medical opinion on the advisability of extraction in patients with bleeding tendencies is stressed.

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BILATERAL MOLAR IMPACTIONS IN CORONOID PROCESSES WITH UNILATERAL MOLAR IMPACTION IN NECK OF LEFT CONDYLE

William Stark, D.D.S., M.S., and Richard P. Keim, D.D.S., M.S., Braddock, Pa.

THE following case report illustrates a bilateral impaction in the coronoid processes associated with unilateral impaction at the neck of the condyle. A cursory search of the literature reveals that no such case has been reported to date.

CASE REPORT

Past History.—On July 16, 1956, a 64-year-old white woman was referred by her physician for examination and consultation. Her chief complaint was bilateral earaches. The patient presented a series of lateral-jaw and anteroposterior skull radiographs taken by her physician in his attempt to diagnose recurrent earaches of two years' duration. The physician's radiographic report indicated bilateral molar impactions in the coronoid processes. This patient was referred to the local hospital for additional skull radiographs. The roentgenologist's findings were as follows: "Radiographic examination of mandible reveals a tooth erupting through the sigmoid notch bilaterally. On the left there is a destructive process above the apex. The remainder of the mandible is edentulous." (Figs. 1, 2, and 3.)

The patient was admitted to the hospital on Aug. 26, 1956, for treatment.

Physical Findings.—The general physical findings were essentially negative. Blood pressure was 120/80; pulse rate was 80 per minute; and temperature was 98.4° F.

Laboratory Findings.—Urinalysis was negative. Examination of blood revealed 4,120,000 red blood cells; 7,700 white blood cells; polymorphonuclear neutrophils, 67 per cent; lymphocytes, 29 per cent; monocytes, 4 per cent; bleeding time, three minutes; and coagulation time, four minutes.

Preoperative Diagnosis and Treatment.—The patient was found to have bilateral molar impactions in the coronoid processes. Surgical removal of these impactions was scheduled for August 29, with routine preoperative orders.

Operation.—On August 29, at noon, the patient was premedicated with morphine sulfate, ⅙ gr., atropine sulfate, 1/150 gr., and Seconal, 1.5 gr. Under Pentothal sodium endotracheal anesthesia, the face and oral mucosa were prepared with tincture of Zephiran. The jaws were separated with a Molt mouth prop. The index finger was used to palpate and trace along the right external oblique ridge, up the anterior border of the ramus, to the head of the coronoid process. With a No. 15 Bard-Parker blade, an incision was made, starting at the head of the coronoid process and going down along the anterior border of the ramus and the crest of the external oblique ridge to the third molar region. A mucoperiosteal flap was reflected and, by palpation, the impacted tooth was located and outlined. The bone was found to be bulging on the medial surface of the coronoid process. A thin layer of the overlying bone was removed with a chisel and mallet. Thus, the tooth was exposed

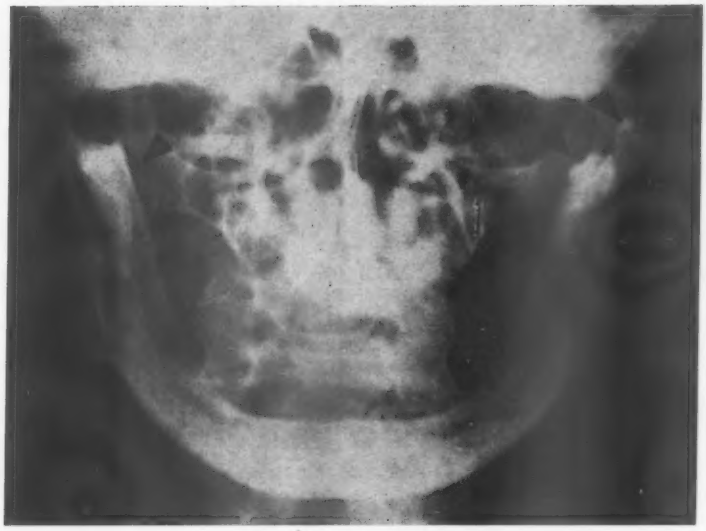

Fig. 1.—Preoperative roentgenogram.

Fig. 2

Fig. 3

Fig. 2.—Preoperative roentgenogram.
Fig. 3.—Postoperative roentgenogram.

Fig. 4.—Postoperative roentgenogram.

adequately and was removed from its socket by means of an exolever. The delivery of this tooth was made relatively simple by the presence of a destructive bone process caused by infection. The wound was débrided with curettes; sharp processes were removed with rongeur forceps and files. The tissues were approximated and sutured with interrupted 000 silk. A similar procedure was followed on the left side. The patient left the operating room in good condition.

Course.—The patient had a relatively uncomplicated postoperative course. Considerable bilateral facial edema subsided in several days. The patient experienced little pain and discomfort. Radiographs were taken on the third postoperative day. The radiographic report revealed the outline of the areas of the recently removed teeth. In addition, these radiographs showed the presence of a molar in the neck of the left condyle (Figs. 3 and 4). No surrounding bone destruction was evident around this tooth. The presence of this condylar impaction was missed in the preoperative radiographic survey by the physician, the hospital roentgenologist, and the surgeons. After further consultation, it was decided that because of the absence of bone destruction, the precarious position of this remaining impaction, and the weakening of the bone by the recent surgery, removal of this tooth should be deferred. The patient was discharged on the fifth postoperative day, to be followed at the office. To date, postoperatively, there have been no recurrent earaches. Recent roentgenograms reveal normal healing.

DISCUSSION

A case of bilateral impactions of third molars in the coronoid process of the mandible associated with a unilateral condylar impaction has been presented. It is important to note that the physician, the roentgenologist, and the surgeons erred in their preoperative diagnosis by not noting the condylar impaction. However, the patient's chief complaint has been alleviated, and surgical removal of the condylar impaction is not considered necessary.

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UNUSUAL MANDIBULAR IMPACTIONS

Report of a Case

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THE patient, an 18-year-old airman, presented himself to the dental clinic complaining of soreness in the right posterior area of his mandible. Clinical examination revealed a complete dentition, except for the right mandibular molar area where a flap of soft tissue covering the mesial half of a partially erupted molar tooth was being traumatized by an extruded maxillary right second molar. The patient denied knowledge of extraction of any of his teeth. An intraoral radiograph showed an indistinguishable mass of teeth (Fig. 1).

Fig. 1.

A lateral head plate and anteroposterior films were taken for better visualization of the area (Figs. 2 and 3). The lateral radiograph demonstrated three molars embedded in the body of the mandible near the angle. The roots of the lower or most inferior molar (first molar) appeared to be well formed and

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Fig. 2.

Fig. 3.

showed a close approximation to the inferior border of the mandible and the mandibular canal. Because of the extreme extrusion of the upper molar, this tooth was extracted.

PERIODONTIA

. . . . . .

STUDIES ON A BACITRACIN PERIODONTAL DRESSING

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Following periodontal surgery, the main objectives are to obtain optimal healing and to ensure a minimum amount of discomfort to the patient. Histologic studies[8, 9] have borne out the clinical impression that, following a gingivectomy, at least partial epithelization occurs in approximately one week and complete covering ensues shortly afterward. In a healthy person who is already healing at an *optimal* rate, there is probably very little that one can do to increase this rate of healing. In order to reduce patient discomfort, however, a better postsurgical periodontal dressing is desirable. Smears taken from areas under periodontal dressings that had caused discomfort to the patient by producing a foul odor and bad taste have shown that an abundance of bacteria was present. Therefore, since some of the bacteria present were probably implicated in causing this disturbance, it was thought that an antibiotic incorporated into a postsurgical dressing might overcome this problem.

In vivo[1] and in vitro[2] studies have shown that the commonly used periodontal dressings possess little antibacterial properties. The purpose of this investigation, therefore, was to try to develop a periodontal dressing which would possess antibacterial properties and at the same time be stable at room temperature.

Predeterminations concerning the properties of bacitracin suggested that this substance might be useful in periodontal dressings. These properties are as follows: (1) bacitracin rarely produces sensitivity after repeated doses; (2) it is not inactivated in the presence of the enzymes studied to date; (3) it is not inhibited by organisms which produce penicillinase; (4) it is bactericidal as well as bacteriostatic; (5) it has a wide spectrum of antibiotic activity; and (6) it is not inhibited by necrotic tissue, pus, exudates, secretions, and blood serum.

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Its greatest usefulness is in topical therapy, for it is nephrotoxic when administered parenterally and inactivated when given orally.

Tannic acid, which is a component of most periodontal dressings presently in use, is said to be one of the organic acids capable of inactivating bacitracin.[3] The first series of experiments was devised to determine whether this was true and, if so, then whether a dressing in which powdered Gelfoam was substituted as a hemostatic agent for tannic acid would overcome this difficulty.

EXPERIMENTAL

Part I.—The formulas for the powder portion of the dressings tested are as follows:

Powder A (Standard Dressing):

Zinc oxide	165 Gm.
Rosin, powdered	210 Gm.
Tannic acid	15 Gm.

Powder B (Standard Dressing Containing Bacitracin):

Same formula as powder A, except that, in addition, it contains 500 units of zinc bacitracin per gram

Powder C (Experimental Dressing):

Zinc oxide	49.5 Gm.
Rosin, powdered	63.0 Gm.
Gelfoam, powdered (Upjohn)	2.0 Gm.

Powder D (Experimental Dressing Containing Bacitracin):

Same as powder C, except that, in addition, it contains 500 units of zinc bacitracin per gram

All powders were passed through a No. 60 sieve. It was found that this step was very important for producing desirable physical properties. The liquid portion used consisted of:

Lump rosin	7.5 Gm.
Almond oil, sweet	30.0 ml.
Eugenol	60.0 ml.

The leaching-out effect which saliva might have on the antibiotic incorporated in the dressing was studied by placing the dressings in a synthetic saliva at 37° C., for periods of one, seven, and fourteen days before testing them on seeded plates.

The formula[10] of the synthetic saliva used was as follows:

Solution A (X100)

$CaCl_2H_2O$	22 Gm.
NaCl	58.4 Gm.
$MgCl_2 \cdot 6\ H_2O$	8.12 Gm.
HCl	16 c.c.
$H_2O_{q.s}$	1,000 c.c.

Solution B (X100)

K_2HPO	0.5 molar
$H_2O_{q.s}$	1,000 c.c.

The effects of the antibacterial action were also studied by comparing the effects of a freshly prepared dressing to those of dressings which were prepared and kept at 37° C. for four, seven, ten, and fourteen days previously.

Small pellets of each of these dressings were placed in a Petri dish containing a solidified culture medium which had been seeded with fresh saliva before pouring. The formula[10] for the media used was as follows:

Water	980 ml.
Proteose peptone #3	20 Gm.
Yeast extract	5 Gm.
Dextrose	2 Gm.
Agar	20 Gm.
Synthetic saliva, Solution A	10 c.c.
Solution B	10 c.c.
Trace element solution	1 drop

The plates were incubated at 37° C., and the radius of the zone of inhibition was read and recorded in millimeters at twenty-four- and forty-eight-hour intervals. All tests were run in triplicate.

Findings:

1. Periodontal dressings (dressings A and C) which contained no antibiotic exhibited little or no inhibitory zone (Table I).

TABLE I. ZONE OF INHIBITION (IN MM.)

DAYS	POWDER A CONTROL	POWDER B CONTROL + BACITRACIN	POWDER C EXPERIMENTAL	POWDER D EXPERIMENTAL + BACITRACIN
Fresh	1.5	3.5	1	5
4	0	3.5	0.5	4.5
7	0.5	3	0	4
10	0	3	0.5	4.5
14	0	3	1	5
	Leached With Artificial Saliva			
1	0	4	0.5	5
7	0.5	1.5	0	3
14	0	0	0	4

2. Periodontal dressing B, which contained zinc oxide, rosin, tannic acid, and 500 units of zinc bacitracin per gram, exhibited little antibacterial effect after being leached out with a synthetic saliva for periods of either seven or fourteen days.

3. Periodontal dressing D, which contained zinc oxide, Gelfoam, rosin, and 500 units of zinc bacitracin per gram, had surrounding zones of inhibition averaging 3.5 mm. at the end of fourteen days. Leaching out with a synthetic saliva had little or no effect on its antibacterial properties.

Part II.—To investigate the effect of increased amounts of bacitracin on the antibacterial action of the dressing, the following "powders" were tested in the manner previously described:

Powder E:

Zinc oxide powder	99.0 Gm.
Rosin, powdered	126.0 Gm.
Gelfoam powder	4.0 Gm.
Zinc bacitracin powder 58.8 units per milligram	11.68 Gm.
(3,000 units of zinc bacitracin per gram of the other ingredients)	

Powder F:*

Zinc oxide	1 part
Zinc bacitracin	2 parts
Rosin, powdered	1 part

Powder G:

Pure zinc bacitracin

Powder H:

Pure zinc bacitracin plus the liquid portion of the dressing

Findings: Powders E, F, G, and H produced respective zones of inhibition as follows: 7.5 mm., 10.0 mm., 10.0 mm., and 7.5 mm. These results, therefore, indicated that powder E, which contained 3,000 units of bacitracin and in addition permitted the incorporation of a hemostatic agent, was probably the dressing of choice. The data, however, also indicate that the eugenol component has some inactivating effect on the zinc bacitracin.

Part III.—To test the validity of the above finding, three bacitracin-impregnated paper disks were placed on a Petri dish containing the media already described. One disk contained 100 units of bacitracin, one contained 100 units of bacitracin plus one drop of the eugenol mixture, and one disk contained 100 units of bacitracin plus two drops of the eugenol-containing liquid. The plates were incubated overnight at 37° C.

Findings: The results, shown in Table II, demonstrate that eugenol has a slight inactivating effect on bacitracin. Clinically, therefore, it would seem wise to use as stiff a mixture as possible.

TABLE II. ZONE OF INHIBITION (IN MM.)

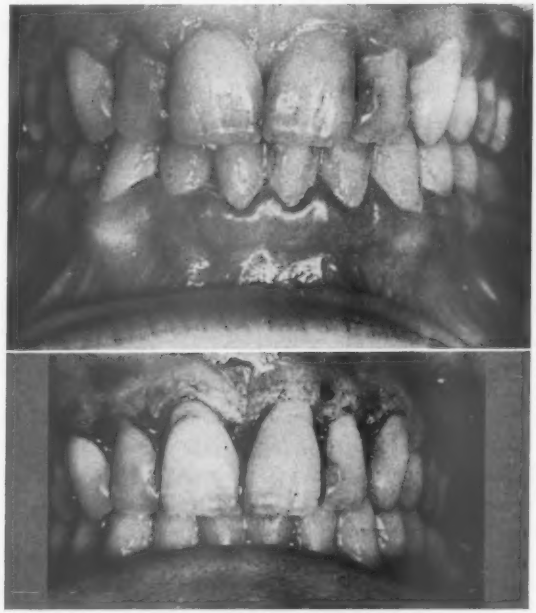
Bacitracin paper disk containing 100 units	12
100 unit disk + 1 drop of liquid portion	10
100 unit disk + 2 drops of liquid portion	8

*This gives the dressing a concentration of approximately 28,000 units of bacitracin per gram.

Part IV.—In a clinical investigation, experimental dressing E, which contained 3,000 units of bacitracin per gram, was used as a postsurgical dressing. Patients with a diagnosis of gingivitis or periodontitis, who required a gingivectomy as part of their periodontal therapy, were used as the subjects.

The initial tests were run to obtain information on allergic reactions, fungus infections, healing rate, and patient comfort.

A.



B.

Fig. 1.—*A*, Preoperative view. Curettage was done, and the case was re-evaluated before further therapy was undertaken. *B*, A gingivectomy was necessary on the maxillary arch. This photograph was taken immediately following surgery.

In the first 100 cases the bacitracin dressing was used. In the next 100 consecutive cases the control dressing, which contained no antibiotic, was used. All packs were left on for one week. The results were as follows:

1. No allergic reactions occurred in either group.

2. Healing appeared to be taking place at an optimal rate in both groups.

3. In the bacitracin dressing group, one patient, the fourteenth person in the series of 100 cases, developed a Monilia infection on the buccal mucosa opposite the dressing. This area was completely healed in seven days, however, with no therapy other than removal of the dressing.

4. To test patient comfort, the following question was asked: "Were you aware of any unpleasant odor or taste this past week?" In the bacitracin group,

83 per cent of the patients were unaware of any such sensations, and 17 per cent were uncertain. In the control series, on the other hand, 25 per cent complained of their food being unpalatable because of a bad taste from the dressing (even before the question was asked), while 58 per cent replied "Yes," 10 per cent were uncertain, and 7 per cent were unaware of anything unusual.

A clinical impression was obtained, from the foregoing cases, that the teeth were less stained and that the pack itself was cleaner in the bacitracin group than in the control series. To test the validity of this observation, in the next fifty consecutive cases a controlled experiment was run as follows: After the gingivectomy was completed (Fig. 1), a control dressing was placed over an

Fig. 2.—Control pack in place.

Fig. 3.—Bacitracin pack in place. *C*, Control pack; *T*, bacitracin pack.

area involving a minimum of three teeth (Fig. 2), while the bacitracin dressing was placed over the remaining area (Fig. 3) which also contained a minimum of three teeth. At the end of one week both dressings were removed (Figs. 4 and 5). The results were as follows:

1. In every case the teeth were cleaner and less stained on the bacitracin side.

2. In every case the debris, both under and around the bacitracin dressing, was much less than that about the control dressing.

3. No allergic reactions or fungus infections occurred in any patient.

Fig. 4.—Bacitracin dressing is on left, control is on right. Bacitracin dressing is, in general, much cleaner in appearance than control.

Fig. 5.—Appearance of teeth and gingival tissues immediately after removal of dressings. Teeth and tissues on left, which were under the bacitracin dressing, are less stained and generally cleaner in appearance than those under the control on the right.

In an additional fifty cases the bacitracin dressing was used alone, and all the above findings were confirmed. No additional cases of fungus infection have since occurred.

The above findings have been summarized in Table III.

TABLE III. PERCENTAGE OF CASES ASSOCIATED WITH THE CONDITIONS INDICATED

CONDITIONS	BACITRACIN DRESSING	CONTROL DRESSING
Allergic reactions	0	0
Fungus infections	0.5	0
Healing optimal	100	100
Were you aware of any unpleasant odor or taste in your mouth?		
Yes	0	83
Uncertain	17	10
No	83	7
Teeth appeared cleaner	100	0
Debris under and around the dressing was less	100	0

DISCUSSION

Linghorne and O'Connell,[5] in studying the therapeutic properties of periodontal dressings, came to the conclusion that they were effective bacteriostatic agents against *Staphylococcus aureus, Streptococcus viridans, Streptococcus hemolyticus, Micrococcus catarrhalis,* and *Candida albicans.* They further concluded that the addition of 5 per cent sulfathiazole or penicillin (5,000 units to 5 grams of pack) did not seem to increase the bacteriostatic effectiveness of the pack.

Our findings are contrary to theirs and lend further support to our earlier findings,[2] as well as those reported by Fraleigh,[1] that periodontal dressings that contain no antibiotic have little or no antibacterial effect. These differences may be explained in part by the fact that in our present study, and in that of Fraleigh, the dressings were tested against the organisms found in whole saliva, while Linghorne and O'Connell tested them against single organisms.

It also becomes apparent from our data that eugenol has some inactivating effect on bacitracin, and, therefore, it would seem advisable to use as stiff a mixture as possible in order to incorporate a maximum quantity of powder. The findings obtained confirm the observation previously reported[3] that tannic acid does inactivate the bacitracin present. The absence of allergic reactions to the topical use of bacitracin is also in accord with previously published data.[6]

In a recent report on the tissue reaction to a gingivectomy pack in dogs,[9] Waerhaug reports the presence of a necrotic membrane between the periodontal dressing and the epithelium. His findings were all based on histologic observations. Although histologic studies were not done in this present investigation, in our study of gram-stained and methylene blue smears from the tissues under the dressings, we observed no membrane that seemed comparable to that described by Waerhaug. The necrotic membrane observed by Waerhaug may have been due to either (1) a necrosis caused by excessive pressure as a result of the acrylic splints he used to maintain the dressing in place or (2) leaving the pack on for too long a period of time (they were on from nine to twenty-three days). Unpublished clinical observations of several investigators would implicate the acrylic splint as the probable cause of the necrotic membrane.

The absence of stains on the teeth is probably due to the absence of tannins in the experimental pack. The other beneficial results observed may be attributed to the antibacterial effect of the bacitracin.

Bacitracin is not absorbed from the gastrointestinal tract to any appreciable extent, even when large amounts are administered by mouth; therefore, there is no danger of nephrotoxicity from its use topically.[7] Most of a given oral dose is inactivated in the bowel.

CONCLUSION

As a result of this investigation, it is felt that a dressing containing 3,000 units of bacitracin per gram is an effective postgingivectomy pack. It is stable at room temperature, it is easy to use, and it affords maximum patient comfort.

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A PILOT STUDY OF A SEROLOGIC FACTOR IN PERIODONTAL DISEASE

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OVER thirty years ago, during the course of their studies on the association between bacteria and periodontal disease, Hall and Howitt[1] found that human sera would agglutinate suspensions of the organism *Micrococcus gazogenes.* This organism is a minute, anaerobic, gram-negative coccus which can be readily isolated from the gingival crevice. Under the current bacterial nomenclature[2] this species of bacteria is known as *Veillonella gazogenes.* Hall and Howitt were studying a small group of convicts in San Quentin prison and they found that, in general, those men with "pyorrhea" had a lower serum Veillonella agglutinin titer than the men with healthy gingivae. This finding led them to suggest that the serum Veillonella agglutinin titer and resistance to periodontal disease were directly related. The investigation reported here represents an attempt to substantiate the findings of Hall and Howitt.

Two groups of adults, twelve women and twelve men in each, were studied. Patients undergoing treatment in the Department of Periodontia of the University of Oregon Dental School formed the study group. They all exhibited marked periodontal pocketing and were selected by Dr. F. G. Everett and his staff. The control group consisted of faculty members and dental students, all of whom were periodontally healthy and had no history of gingivitis.

A saliva specimen was collected from each subject in the study, and a strain of Veillonella was isolated by the method described by Sims and Snyder.[3] These strains were subcultured twice on plates of Douglas lactate agar[4] to ensure purity. Each strain was inoculated onto two slants of Douglas lactate agar and incubated for forty-eight hours to provide a sufficient suspension of cells for agglutination tests.

By the normal venipuncture technique, 5 ml. of blood was obtained from each subject. The blood was placed in a 15 ml. centrifuge tube, allowed to clot at room temperature, and then refrigerated overnight. The clot was loosened with a sterile glass rod, and then the tube was centrifuged for fifteen minutes to obtain a clear serum. The serum was stored in small sterile test tubes, one drop of a 1 per cent solution of Merthiolate in borax being added as preservative.

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The agglutination tests were set up in the usual manner, using 13 by 100 mm. serologic tubes. The range of the serial dilution series was 1:2, 1:4, 1:8, 1:2,048. For preparing the serial dilutions and the antigen cell suspensions, 0.4 per cent sodium chloride solution was used. Higher concentrations of saline caused spontaneous agglutination in the control tube. The tests were incubated overnight at 50 to 55° C., as earlier work using rabbit serum had shown that this was the only way to obtain reproduceable results. Readings were made in daylight with the aid of a hand lens. Agglutination was recorded as either positive or negative for a given tube; that is, anything less than the conventional 4 plus agglutination was recorded as negative.

TABLE I. COMPARISON OF THE SERUM VEILLONELLA AGGLUTININ TITER OF A PERIODONTALLY DISEASED GROUP OF ADULTS WITH A PERIODONTALLY HEALTHY CONTROL GROUP

STUDY GROUP				CONTROL GROUP			
CASE NO.	AGE	SEX	TITER	CASE NO.	AGE	SEX	TITER
P1	29	F	1:16	C1	26	F	1:32
P2	42	F	1:8	C2	23	F	1:64
P3	41	F	1:8	C3	23	F	1:8
P4	45	F	1:16	C4	42	F	1:32
P5	23	F	1:32	C5	25	F	1:32
P6	48	F	0	C6	26	F	1:8
P7	40	F	1:32	C7	38	F	1:2
P8	36	F	1:16	C8	32	F	1:32
P9	25	F	1:4	C9	40	F	1:8
P10	35	F	1:64	C10	40	F	1:8
P11	29	F	0	C11	47	F	1:64
P12	36	F	1:64	C12	42	F	1:16
P13	35	M	1:16	C13	30	M	1:8
P14	31	M	1:8	C14	26	M	1:16
P15	50	M	1:16	C15	34	M	1:4
P16	41	M	0	C16	30	M	0
P17	33	M	0	C17	35	M	1:32
P18	48	M	1:16	C18	36	M	1:64
P19	36	M	0	C19	34	M	1:4
P20	46	M	1:8	C20	29	M	1:16
P21	57	M	1:16	C21	32	M	0
P22	34	M	1:8	C22	31	M	1:2
P23	36	M	1:32	C23	30	M	1:32
P24	38	M	1:8	C24	53	M	1:8
Mean	38.0		1:16.2		33.3		1:20.5

Table I lists the age last birthday, sex, and agglutinin titer for each subject in the study. Inevitably, the scarcity of older persons with healthy gingivae has resulted in a lower mean age for the control group. The mean agglutinin titer of the control group is slightly higher than that for the study group, but the difference is not statistically significant when tested at the 5 per cent level. On the basis of these results, the hypothesis that the serum Veillonella agglutinin titer is a factor in periodontal disease must be rejected. However, the fact that parenteral exposure to a given organism in the mouth can be detected by examining the serum for antibodies of low titer is not without interest. Studies similar to that described here but concerned with the other oral microorganisms could very well be more rewarding.

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ORAL MEDICINE

INTEGRATED BEHAVIOR IN CONNECTIVE TISSUES

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CONNECTIVE tissues are dispersed throughout the organism in anatomic and chemical contiguity. They form a biologic continuum which has graded physical properties, varying from the liquidity of synovial fluid, to the looseness of skin, to the denseness of cartilage, bone, and dentine. Many of the mechanical and physiochemical properties of connective tissue are identified with the extracellular part which comprises two major sets of components: (1) a fibrillar portion made up of reticulin, collagen, and elastic fibers and (2) a nonfibrillar matrix, the ground substance, including electrolytes and water.

The most intimately studied element of the fibrillar part has been the collagen. Over the past decade or so, with the development of electron microscopy, the ultrastructure of the fibril has been visualized. The most prominent characteristic is the cross-banding or regular striation of the fibril at intervals of 640 angstroms. Recently the reticular fibers, which are finer than collagen and which stain with silver (collagen does not), have been shown to be related to collagen, probably as the precursor.

Probably the fibers and the interfibrillar substances are related as components of an integral unit or very large molecule, but this relationship has not been clearly defined by the harsh and disruptive methods generally applied to the microscopic and submicroscopic studies of tissues. Nevertheless, the analytic approach may be a necessary precursor to the synthetic view. In our laboratory we have attended somewhat more to the nonfibrillar ground substance.

Ground Substance.—The ground substance appears to be optically homogeneous. Dr. Bondareff, working in Isidore Gersh's laboratory, has recently presented evidence showing this apparently amorphous material to be organized at the submicroscopic level. Chemically it has been partially characterized

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by the presence of carbohydrate-containing protein(s), called mucoproteins and glycoproteins, and by the mucopolysaccharides. The distribution of the ground substance can be demonstrated in sections from tissues which are appropriately fixed, that is, where chemical fixatives are avoided and where the tissue block is frozen at very low temperatures and then dehydrated in a vacuum. This is termed freezing-drying fixation. There are fairly specific histochemical procedures which color the histologic sections by virtue of the stainability of carbohydrate-containing components of the ground substance. The most satisfactory method employs periodic acid to oxidize the carbohydrate groups. This is followed by treatment with a colorless reagent, leucofuchsin (the Schiff reagent), which then stains these reacting groups. In their classic study on ground substance, Gersh and Catchpole postulated that the intensity with which a tissue stained was related to the concentration of the reacting aldehyde groups and to the state of aggregation of the ground substance. Loose tissues, such as those of embryonal connective tissue or of young tooth pulp, are lightly stained with these reagents. Denser, more highly aggregated tissues, such as those of skin and of gingiva, are more intensely stained. Epiphyseal cartilage and young bone or young dentine stain intensely. Such highly aggregated, dense structures as mature bone, dentine, and cementum are only lightly stained or virtually unstained. In this latter example, the characteristic carbohydrate groups ordinarily responsible for the reaction are presumed to be masked or protected from oxidation by the periodic acid in some way, possibly by the cross-linking which is characteristic of many high polymers, including biologic polymers.

In order to describe the microscopic distribution of the glycoproteins of the ground substance in a representative tissue, I have chosen as an example the free gingivae. In frozen-dried preparations one sees an irregular demarcation separating the epithelium from the underlying connective tissue. This undulating line stains intensely with the periodic acid method. It is called the "basement membrane." On refined examination, this structure can be shown to consist of a zone of ground substance containing embedded reticular fibers. The organization and staining of this structure serves as a coarse criterion of the general state of the contiguous connective tissue. In the subepithelial layers below the basement membrane lie the connective tissue cells and the collagen, reticular fibers, and elastic fibers, embedded in the ground substance. These layers react with the stain to give a pink, red, or magenta color. A related pattern of ground substance-fiber contiguity is observed in other connective tissues, such as those of pulp, skin, monkey sex skin, avian comb, large blood vessels, etc. In the connective tissue meshwork the small blood vessels are delineated by a deeply stained peripheral basement membrane.

Two-Phase System.—If microscopic sections of frozen-dried tissues are first bathed in water and then stained to demonstrate the ground substance, they may appear to be less intensely colored. This easy test shows that the connective tissue contains fractions which are soluble in water. At the very

simplest, then, the connective tissue ground substance contains two phases—one which is soluble in water and another which is insoluble. It can be shown that the relative amounts of these two phases vary according to the tissue or with physiologic and pathologic changes in any tissue.

Carbohydrate-Containing Components of Ground Substance.—In the chemical analysis of connective tissue the findings parallel the aforementioned histochemical results; water-soluble and water-insoluble carbohydrate-containing fractions coexist. Meyer and his collaborators have devoted many years to the chemical identification of some of the important carbohydrate components of connective tissue. Prominent substances are hyaluronic acid and chondroitin sulfate. In the former the carbohydrates, glucosamine and glucuronic acid, are linked together in equal parts; in chondroitin there are equal parts of galactosamine and glucuronic acid. These fundamental carbohydrate units are repeated many times in these macromolecules or polymers. It is not known how these carbohydrates, called mucopolysaccharides, are tied to the protein of the structure, but they appear to be held together in some sort of close relationship.

Colloidal Properties of Connective Tissue.—These morphologic, histochemical, and chemical aspects of connective tissue formed a basis for some understanding of its physicochemical behavior. The organization into large molecules lends colloidal properties to the matrix. Some parts of the carbohydrate moieties, notably the carboxyl (COOH) and the sulfate (SO_4) groups, render the colloid negatively charged at physiologic pH. The presence of water-soluble and water-insoluble parts characterizes this biologic system as a heterogeneous colloid, a two-phase system, consisting of a colloid-rich, water-poor phase which is in equilibrium with a colloid-poor, water-rich phase. The significance of these phases in some biologic states will be elucidated later.

TABLE I. RELATIONS BETWEEN COLLOID CHARGE DENSITY AND STAINABILITY IN SOME CONNECTIVE TISSUES

TISSUE	STAINING WITH PERIODIC ACID-LEUKOFUCHSIN	DENSITY OF NEGATIVELY CHARGED COLLOID IN EQUIVALENTS
Synovial fluid	Faint pink	0.001
Skin	Light pink	0.050
Gingiva	Pink	0.095
Cartilage	Red	0.165

Using an electrochemical method, we have succeeded in measuring in a quantitive way the density of the fixed, negatively charged colloid in various connective tissues. We have expressed this as the number of equivalents of immobile negative charge per kilogram of water in the tissue. Our electrometric results fit well with the morphologic, histochemical, and chemical evidence; that is, loose, faintly stained structures with relatively greater amounts of water-soluble ground substance contain a low density of negatively charged colloid. Denser tissues more deeply stained contain higher concentrations of charged colloid and relatively smaller amounts of water-soluble material.

Very dense connective tissues, such as mature bone or dentine, which are virtually unstained by the periodic acid-Schiff method and which contain very little soluble material, show the greater density of negatively charged colloid. In Table I these correlations are recorded for a few of the connective tissues which we have studied.

Interaction of Connective Tissues With Water and Charged Substances.— Because of the negative charge on the biologic colloid, it gains unique properties affecting water and salt distribution in tissues. This can be understood from the work of two great physical chemists, Gibbs and Donnan. A dissolved charged protein or colloid separated from a salt solution by a membrane which permits passage of the salt and water only (semipermeable membrane) will tend to concentrate within itself those mobile salt ions of opposite charge. This principle can be extended to the description of the behavior of the negatively charged connective tissue colloids. Such physiologic ions as positively charged sodium, potassium, calcium, and magnesium should be concentrated in tissues where the ground substance is highly aggregated, that is, where the negative charge is dense. Organic molecules which carry positive charges are similarly concentrated. To generalize, it may be said that the denser, more highly aggregated or polymerized ground substance contains high concentrations of positively charged ions. This ion-concentrating property operates in a selective fashion. Thus, potassium is preferred to sodium. Bivalent (+2) and trivalent (+3) ions are concentrated according to the square and cube of their concentrations, respectively.

Another kind of interaction of connective tissue colloids with positive ions also occurs. This depends upon the formation of bound complexes, such as calcium colloid and magnesium colloid, between the protein and the positively charged electrolyte. Foreign cations, such as lead and strontium, can be deposited in this way. Positively charged organic molecules behave similarly, and complexes involving glucosamine, amino acids (histidine, arginine, and lysine), amines (histamine), vitamins (thiamine), hormone precursors (tyramine and tryptamine), drugs (procaine) and even large protein molecules (protamine) can be formed. In these cases, also, the reactions are selective, some substances being more readily accepted than others.

In these interactions between the negatively charged colloids of connective tissue and the positively charged electrolytes (cations), energy is released. Thus, sodium ion Na^+ + colloid$^-$ = Na colloid → energy; histamine + colloid = histamine colloid → energy. These releases of energy are termed the "free energy" of the reactions, and they are expressed in calories. In the presence of a number of different inorganic and organic cations the relative amount of each accumulated in the colloid is related to the energy released by the binding reactions of each.

In the combination of calcium with the ground substance, more energy is released than can occur in the interaction between sodium and ground substance. For this reason, calcium will replace sodium from its combination with the colloid and additional energy (2,300 calories) is released. Lead will

displace calcium from its combination releasing 1,200 calories. The ions can be listed in the order of increasing displacing potential as follows: sodium, potassium, calcium, magnesium, strontium, lead, organic cations, ammonium ion.

These exchanges of ions are known as "ion exchange reactions," and the connective tissues behave as do ion exchange resins. The water softeners used in homes are familiar examples of this kind of system. Here the calcium ion in the incoming water is preferred to sodium, which is present in the column of softener, so the sodium is driven off in the outflowing water and the calcium is retained on the resin in the cylinder.

The Milieu Interieur and the Extracellular Compartment.—Virtually all parenchymatous cells are in close proximity or are coated by the ground substance. In a morphologic and a physicochemical sense, the connective tissue ground substance occupies a strategic position in its relation to blood and to parenchymatous cells. The matrix acts as an intermediate substance interposed between the cells and the blood, thus constituting the true *milieu interieur.* Tissue fluids are coextensive with this matrix, constituting an integral part of its water-rich phase. Through the gel of ground substance, water, gases, salts, wastes, nutrients, and internal secretions must diffuse in their transfers between the blood and cells. These exchanges are determined by the physical and chemical properties of the ground substance, which is the "extracellular compartment." Ultimately, then, the adjustment for homeostasis is conditioned by the state of the connective tissues.

Blood, the extracellular ground substance, and cells are considered as an integrated system in which water and electrolyte concentrations cannot vary independently. Fluctuations in the concentration of blood levels of any ion must lead to changes in the concentration of that ion in the ground substance and in the cells. As a further corollary, changes in the concentration of any ion in the ground substance are accompanied by readjustments in the concentrations of all the other charged substances. Procedures which modify blood electrolytes (as, for example, the intravenous administration of fluids or the injection into tissues of various solutions) may have wider consequences than has been thought formerly. Also, it will become clear that physiologic or pathologic modification of the connective tissues leading to changes in the density or character of the colloid will in turn affect the ion distributions. There is a cycle of interdependence among the colloid and the various charged components.

Labile Behavior of Connective Tissue.—I have stressed the physical and physicochemical properties of connective tissue. From this, one might infer that connective tissue is relatively inert, but we know that in its biologic behavior it exhibits great lability. Such striking examples may be cited as the immediate swelling of the skin in response to various injuries, changes in tissue hydration and plasticity during pregnancy, the rapid softening of bones in response to parathyroid extract, and the tremendous growth of the avian comb following administration of testosterone. Ultimately, of course, these

changes are ascribed to cellular activity. Connective tissue cells, the fibroblasts, osteoblasts, and odontoblasts, contain cytoplasmic granules of glycoprotein which are presumed to be the precursors of the ground substance. Following administration of such hormones as estrogen, cortisone, testosterone, relaxin, or parathyroid extract, or in tissue growth or injury, the general pattern of response is repeated. It is susceptible to certain unifying concepts which are as follows: (1) The ground substance of the connective tissue responds to stimulation by a process of depolymerization or disaggregation. (2) There is an increase in the water-extractable material, including the carbohydrate-containing fractions. (3) Connective tissue so altered acquires an affinity for certain intravital dyes, such as Evans blue; these then become localized in the ground substance. (4) Water uptake occurs; this increases the plasticity or mobility of the structures and may condition the ensuing growth process. (5) The density of negative charge on the colloids of ground substance falls, and necessarily the salt distribution between blood and connective tissue is modified. (6) With large doses of hormones or in certain disease processes, there may be extensive disaggregation of the ground substance matrix and loss of material; this may be reflected in the composition of blood and urine. All these changes are considered to take place concurrently.

Pubic Symphysis—Relaxin.—The response of the pubic symphysis of the female guinea pig during pregnancy or following the administration of the hormone, relaxin, can be cited as an example of a physiologic process embodying these general changes. In the resting state the symphysis consists of two fibrocartilaginous plates separated by a band of dense connective tissue. When the connective tissue is stained selectively for glycoproteins by the previously described method, the sections show a pink coloration and only small amounts of the glycoprotein dissolve in water. The negative charge density, electrochemically determined, is quite high; the connective tissue ground substance is considered to be highly aggregated or polymerized. Following the administration of small amounts of estrogen and then of relaxin, or during the late stages of pregnancy, the ground substance undergoes remarkable adaptive changes. The connective tissue band becomes broader, almost 1 cm. in width, and its plasticity is increased. Water is taken up in the tissue and the intravitally administered dye, Evans blue, is concentrated at the site. Sections of the tissue stained with the specific periodic acid-leucofuchsin method color intensely red, indicating the first stages in the depolymerization of a highly aggregated structure. There are present considerable quantities of water-soluble glycoproteins. The changes in the density of charged colloid are confirmed by electrochemical determinations at the site. In the serial study of an animal during the sixty-day gestation period, one can follow the gradual lowering of the colloid charge density in the symphysis as parturition approaches; the recovery to normal levels during the first postpartum month can also be traced. In many respects these results are similar to those of Muehlmann, who showed how the mobility of the teeth in pregnant women increased as they approached term. In both instances, the underlying processes may be identical.

Gingiva in Pregnancy.—The gingival changes in women during pregnancy may be cited as another example. The direct relationship between gingivitis in women and the pregnant state has been questioned. From our own work, we have concluded that gingival changes in pregnancy accompany the other somatic changes but often these cannot be detected by the usual clinical examination. If the connective tissue of the gingiva is studied by more sensitive physicochemical methods, however, the alterations are revealed. During pregnancy the colloid density is one-third lower than the normal level and it is not restored until some months after parturition. In some respects, the change in colloid charge density follows that observed in the guinea pig pubic symphysis. Where such local factors as poor hygiene, irregular contact, or poor restorations are also present the occult subclinical changes may become apparent. Upon histochemical study of sections of gingiva in which the "pregnancy gingivitis" is present, the characteristic signs of depolymerization of the ground substance are evident: lessening of stainability of the ground substance, attenuation of the subepithelial and perivascular basement membranes, and increased amounts of water-soluble glycoproteins. This same pattern of change also occurs in the parapuberal type of gingivitis.

Desquamative Gingivitis.—In pathologic states the ground substance changes may become intensified and sometimes irreversible. Let us consider, as an example, the events in desquamative gingivitis (or gingivosis). The gingivae are red and swollen. There are usually bullae and raw areas; on the slightest manipulation, the epithelium peels off from the submucosal layers. From both electrometric studies and histochemical observations, it may be concluded that in this condition the connective tissue is profoundly affected. The interepithelial cement is dissolved, the glycoprotein ground substance is disaggregated, and the subepithelial and vascular basement membranes are destroyed. The water-soluble mucoprotein fraction is increased. At the same time there is an uptake of water (edema) as well as a change in the electrolytes of the tissue.

Relations Among Tissue, Serum, and Urinary Glycoproteins.—The manifestation of connective tissue disease may be protean; this follows from the ubiquitous distribution of the ground substance in the parenchymatous and supporting tissues. For this reason, one might expect that evidence of disease would be signaled by changes in the blood. In persons with arthritis, rheumatic fever, tuberculosis, and cancer the concentration of carbohydrate-containing proteins in the serum is elevated. This might appear to be an utterly nonspecific accompaniment of disease; yet in all of these diseases there is involvement of the connective tissue, either directly or through its role as contiguous stroma.

Gersh and Catchpole suggested that the rise in serum carbohydrate-containing proteins represents the diffusion of soluble depolymerized components of connective tissue into the blood. There has since accumulated some experimental evidence to support this hypothesis: (1) In mice bearing transplanted tumors the stroma contains increased amounts of water-soluble material and the blood mucoprotein level is elevated. (2) Experimental scurvy

in guinea pigs is marked by depolymerization of connective tissue ground substance and by an elevated serum mucoprotein level. (3) Following the administration of parathyroid extract in animals, the mucoprotein ground substance of the metaphysial bone is disaggregated, the soluble fraction is increased, and the blood mucoprotein level rises. Recent experiments on patients confirm this observation.

On the basis of limited experimental and clinical evidence, it also appears that similar urinary changes accompany those in the blood. Thus, rats that have received large doses of parathyroid extract excrete in their urine almost three times the normal quantity of mucoprotein. Patients with burns who have suffered the destruction and injury of large areas of connective tissue also excrete increased amounts of mucoprotein in their urine. Kidney stone formation in some persons may be associated with an increased excretion of the mucoprotein which has a strong affinity for calcium.

The earlier methods which we used did not establish the chemical identity of ground substance carbohydrate-protein complexes and those of the blood. More recently, by the injection of one of the serum mucoprotein fractions (orosomucoid) into chickens, Silberberg has succeeded in producing an antiserum to the human blood orosomucoid. This antiserum can be used to titrate quantitatively the blood levels of orosomucoid. Only recently this immunochemical method has been adapted to tissue studies leading to the identification of substances in the connective tissues of nasal polyps and gingiva which react with the antiserum to orosomucoid. This reaction is not due to residual blood but, rather, to soluble proteins in these tissues. Thus, additional evidence of a relationship between the blood and tissue glycoproteins has been established.

The fact that tissue alterations are reflected by blood changes may be of significance in studying dental disease. In paradontosis where there is diffuse loss of the alveolar bone, there is reason to suspect that this is more than a local phenomenon. Perhaps the alveolar bone changes are but the local evidence of a more general disturbance in connective tissue. Serum mucoprotein levels have been determined in a group of sixty-two patients with paradontosis. In 39 per cent the serum mucoprotein level was elevated, while in a comparable group (with respect to age and sex) without roentgenologically evident bone changes only 12 per cent showed elevated levels. This elevation in serum mucoprotein in such a large percentage of patients with paradontosis may signal profound changes in connective tissue, including the bone, representing the disaggregation of the ground substance. Moreover, this blood finding may be of value in differentiating an active process from one in which an irreversible bone loss occurred at some earlier date.

Formation and Resorption of Bone.—Certain of the general principles which have been formulated in the foregoing may be directly applied for the understanding of the behavior of a special kind of connective tissue, namely, bone. We will consider the intimate changes involved in the apposition and calcification of bone and in its resorption. The colloid of bone is conceived to

be highly aggregated, possessing a high density of negative charge. Due to this negative charge, bone matrix attracts and accumulates positively charged organic and inorganic substances. Important among these is calcium. Calcium forms a combination with the proteins or colloids of bone matrix which we call a calcium-protein complex. Also the positively charged calcium ion is concentrated in bone, thereby neutralizing the negative charge. In this way, calcium concentrations which are as much as ten times those in the blood occur in bone, and in this way conditions favorable for the precipitation of calcium phosphate are established. In bone, calcium exists in at least three forms—as precipitated calcium in the form of a phosphate or more complex crystal, as soluble calcium ion, and as the calcium-protein complex. In a similar way magnesium and the nonphysiologic ions, such as strontium, lead, and radium, may be concentrated in the bones.

We have been intrigued by the problem of how these events are reversed and how hard structures such as bone can become soft and undergo dissolution. In microscopic studies of bone the most reliable information is obtained from tissue which has not been decalcified. Then the ground substance of bone can be stained with the reagents which are specific for the carbohydrate-containing substance. With the periodic acid-leucofuchsin reagent young bone stains pinkish red, while mature bone is but faintly tinted. We have speculated that these tinctorial differences are due to differences in the state of aggregation of young and older bone. It is thought that the latter is more tightly aggregated or polymerized, and that, therefore, its reacting groups are involved in linking together of the molecules and they are not free to react with the staining reagents.

Effect of Parathyroid Extract.—In our earliest essays into the question of bone resorption we used parathyroid extract. Large doses of the hormonal extract cause dissolution of bone. In rabbits or rats 500 to 1,000 units administered in twenty-four to forty-eight hours will change completely the character of metaphysial bones, converting it from a hard material to a soft gelatinous mass. Microscopic sections of this bone show that the matrix has been completely altered, the morphology is disrupted, and its chemical reactivity is modified. While the normal bone is only lightly stained, following the hormone it is tinctured reddish pink. This is presumptive evidence of a disaggregation of the ground substance of the resorbing bone. In electrochemical tests on these bones the results show a decrease in the density of negatively charged bone colloid. As a corollary, following the reduction in density of negative charge, smaller amounts of positively charged substances (notably calcium) can be bound. The colloid and mineral of bone go hand in hand; an effect on one produces a related change in the other. Accompanying these changes in connective tissue there are changes in the metabolic activity of the cells which can be demonstrated by studying their respiration.

Pigeon Medullary Bone.—The experimental biologist who induces changes by administering drugs or hormones and then generalizes from these may be justly criticized for making inferences based on interference with Nature.

Mindful of this objection, and also wishing to broaden our point of view, Dr. Laskin and I are now studying bone resorption in the female pigeon during the egg-laying cycle. Here the events of apposition and resorption succeed each other in rapid sequence. For several days preceding the laying of the first egg (a clutch of two eggs is laid in a period of forty to forty-four hours) the hollow marrow cavities are partially restored. After the egg is laid, bone apposition in the marrow cavity is again intensified for perhaps twenty hours. Then the calcification of the shell is accompanied by a period of very active bone resorption which again leaves a large medullary cavity. This is an interesting biologic adaptation in which change in one structure or tissue (bone) and the release of its minerals and ground substance are linked to a totally different function—the mineralization of the shell and reproduction.

The microscopic characteristics of bone from the femur and tibia of these female pigeons have been studied. The bone which is in an appositional phase or in a resting period stains only lightly with the carbohydrate-specific reagent. During the periods of active resorption, however, the spicules are intensely colored and small aggregates of extracellular remnants of bone matrix are seen in the medullary cavity.

These changes in bone ground substance seen in the pigeon are virtually the very same as those which have been described in the rabbit and rat following parathyroid extract. Whenever bone resorption occurs, the degradation of the matrix is likely to follow this same general pattern of change in the carbohydrate-containing protein of the ground substance.

Mechanisms for Resorption.—At this point, after we have some understanding of the nature of the change in bone during resorption, we are perhaps in a better position to think about the mechanisms which might elicit these changes. The fact that bone or other hard structures can be softened by treating them with acid should not lead one astray. It is understandable that the histologists projected from the laboratory preparations in which bone was softened by acid decalcification and assumed that similar events occur in life. This now appears to be an untenable view. The cellular environment is carefully maintained and buffered against any such remarkable changes in pH as would be required to dissolve bone.

It has also been suggested that the liberation of proteolytic enzymes might accomplish the same end. In our experience with a number of proteolytic enzymes, including a bacterial collagenase, it has not been possible to cause the dissolution of calcified bone. Hence, we have been forced to look elsewhere. Others have worked with this question in a somewhat different context (for example, in relation to the ability of mosses to grow on rock and to maintain adequate mineral intake). Mandl, Grauer, and Neuberg, in a series of papers, have considered the general question of the solubilization of insoluble substances in Nature. They have suggested a mechanism which may be useful in explaining many phenomena, including the resorption of bone. There are, in Nature, many substances which can and do form unionized complexes

with calcium. The behavior of these substances parallels that of certain synthetic organic compounds, called chelating agents (from the Greek *chele*, meaning claw), which are used in industry to dissolve metallic precipitates. Among the biologic chelating agents are such compounds as proteins, the nucleic acids, the uronic acids, di- and tricarboxylic acids (including citric acid) and the polyphosphates, such as adenosine triphosphate (ATP). In the presence of these, and at neutral pH, insoluble calcium salts, such as calcium phosphate, are dissolved or prevented from precipitating. These biologic complexing or chelating agents may arise as intermediate substances in the metabolism of carbohydrates, proteins, and fats. They may also represent fragments of the insoluble structures of the cells and extracellular substance which are formed in the normal turnover and renewal of protoplasm or in its destruction. The cell nucleus and cytoplasm can contribute such residues. Degradation products of connective tissue can also act to dissolve calcium salts.

Of bone, it can be said that the tissue carries within itself the seeds of its own destruction. Such solubilizing agents as desoxyribonucleates and nucleates may arise from the nuclei and cytoplasm of its cells, and uronic acids are residues of its ground substance. Citrate constitutes over 1 per cent of its wet weight, being involved both as a structural component and as an intermediate substance in bone-cell metabolism. Accumulation of these substances or their rapid synthesis and turnover in bone might be a mechanism for its resorption. There would thus appear to be many possibilities, limited only by the almost infinite number of products of cell metabolism, for resorptive mechanisms.

The Possible Role of Citrate.—In preliminary studies in our laboratory we have chosen to study the possible role of citrate, a tricarboxylic acid which occupies a central position in metabolism. In carbohydrate metabolism, when glycogen and glucose are completely utilized (that is, when they are oxidized in respiration) an important step in their degradation involves the formation of citrate. Citrate is ultimately oxidized to carbon dioxide and water. The steps in the process, painstakingly worked out by the biochemists, form what is known as the citric acid cycle. In the metabolism of amino acids and fats some of the residues may also pass through this biochemical cycle contributing to the formation of citrate. According to current views, this substance is obviously of the utmost importance in cellular respiration.

In the presence of citrate, insoluble calcium salts, such as the calcium phosphates, are dissolved. Thus, bone powder, which is shaken in a test tube with sodium citrate, is solubilized. Is it not possible that citrate produced by millions of cells on millions of bone and cell interfaces can likewise cause such a dissolution? The evidence for this view remains elusive. There are two supporting bits: (1) In pigeons, during the egg-laying cycle when bone is resorbing, the blood citrate levels rise and then return to normal levels after the clutch of eggs is laid. (2) Considerably greater amounts of citrate can be found in the metaphysial cells of young rabbit bone than in those cells taken from adult bone.

In that special connective tissue, bone, where such important substances in metabolism as citrate, carbohydrate, carbonate, and phosphate are also integral parts of the structure, there is established a link between energy and form and structure.

I have tried to present a unifying concept of connective tissue in which the lability of its biologic behavior mediated through its cells has been related to changes in its physicochemical properties. The connective tissue ground substance is considered as the strategic extracellular intermediate between cells and blood. It plays a dominant part in maintaining homeostasis in the *milieu interieur* through its interactions with water, salts, and charged molecules. At the same time it is capable of great adaptive changes in its physical properties in response to the external environment, internal secretions, growth, and injury.

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PHARMACOLOGY AND THERAPEUTICS

THE EFFICACY OF A PLACEBO AND SEVERAL ORAL ANALGESICS IN THE TREATMENT OF PAIN OF ALVEOLAR OSTEITIS

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PAINFUL alveolar osteitis, the so-called "dry socket," is one of the most common and distressing postoperative complications of oral surgery. Although self-limited, the importance of alveolar osteitis lies in the marked and often protracted disability which it produces by its persistent pain. Therapy is directed primarily toward relief of this pain by both local and systemic treatment.

The study to be reported was undertaken in an attempt to find an effective means of controlling this pain with oral analgesics in ambulatory outpatients. The objective was to provide satisfactory analgesia with minimal side actions. The long duration of this pain also provided an opportunity for a comparison of the relative effectiveness of various analgesics given by mouth. In order to estimate the potency of the analgesics to be compared, a placebo control was included. The high incidence of pain relief which we observed following administration of a placebo in patients with moderate to severe pain of alveolar osteitis was entirely unexpected.

METHOD

All subjects of this study were outpatients of the oral surgery clinic of the Jefferson Davis Hospital and had had dental extractions under local anesthesia. Those patients who returned to the clinic with symptoms and signs of alveolar osteitis, including moderate to severe pain, were included in this study. All local treatment, either by packing or by topical drugs, was withheld. Instead, each patient was given an envelope containing five capsules with instructions to take one capsule by mouth every four hours for pain and to return the following day. On the next visit the patient reported on the efficacy of the medication in relieving pain. If pain persisted, a second envelope containing five capsules was issued with similar instructions. In this

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manner, the patient was treated for five consecutive days with four drugs and a placebo. Not all patients completed the drug series. Only the reports of patients who did return to the clinic were included in these data.

The drugs studied were: (1) acetylsalicylic acid, 0.6 Gm., (2) anileridine dihydrochloride (ethyl-1[4-aminophenethyl]-4-phenylisonipecotate), 30 mg., (3) dihydrocodeine bitartrate, 30 mg., (4) an "analgesic capsule" containing methadone hydrochloride, 2 mg., d-desoxyephedrine, 1 mg., and pentobarbital sodium, 30 mg., and (5) a capsule containing starch (placebo). Anileridine, a phenethyl derivative of meperidine (Demerol), is approximately twice as potent as meperidine on parenteral administration, with no more frequent side actions than meperidine.[1] Dihydrocodeine bitartrate is a derivative of codeine, but it is a more potent analgesic on parenteral administration. Several investigators have shown that 30 mg. of dihydrocodeine administered subcutaneously approached the analgesic potency of 10 mg. of morphine.[2, 3] The "analgesic capsule" contained three drugs for which some degree of analgesic activity has been claimed. Methadone is a well-established potent analgesic with a long duration of action.[4] Pentobarbital sodium, well known as a hypnotic, has been shown to be capable of relieving pain in man.[5] Desoxyephedrine (methamphetamine) is a central nervous stimulant similar in action to amphetamine, which has been considered an analgesic by some investigators.[6]

Early in this study, 60 mg. of anileridine was administered every four hours. Eighteen of the nineteen patients who received this dose of anileridine obtained significant pain relief. However, most patients also complained of excessive sleepiness, dizziness, and nausea. The dose was therefore reduced to 30 mg. for the remainder of the study.

All drugs were distributed in identical sealed envelopes identified only by a code letter. Neither the patients nor the oral surgeons who distributed the drugs and recorded the patients' reports were familiar with the drugs contained. At mid-point in the study the code letters for all drugs were changed. The consecutive order of administration of the five study drugs was randomized among the patients. A random list of the 120 possible orders of administration was devised prior to the study, and serial patients were assigned to these predetermined orders of administration.

All evaluations of pain relief were made by two oral surgeons. Three categories of pain relief were used: most of the pain remained, most of the pain relieved, and complete pain relief. A pain relief score (0, 1, 2, respectively) was then assigned to each patient's report. One score was given for each day of drug trial (five doses). At the end of the study the mean pain relief score per patient for each drug was calculated. The significance of differences between the mean relief scores of the various drugs was determined by the t-test for means of unequal groups.[7]

All patients were also questioned about drug effects aside from pain relief. Only nonspecific questions were asked, such as "Did the medicine have any other effects?" No suggestion was given as to what side actions might occur, and no check list of specific symptoms was used. The significance of the differences in the incidence of side actions between drugs was estimated by the rank method for paired and for groups of replicates of Wilcoxon.[8]

RESULTS

Only forty-one of the 100 patients included in this series received all five drugs. When the data on these forty-one patients were analyzed as a block, the estimate of the relative analgesic potency of the drugs studied did not differ greatly from that gained from the total data. Therefore, the data on 100 patients will be considered here.

Sixty-seven patients received a placebo; of these, forty-one (61 per cent) obtained adequate pain relief (most pain relieved or complete pain relief). The mean pain relief scores per patient for all drugs studied are presented in Table I. The order of effectiveness of the various drugs is indicated by their relative scores. All drugs except acetylsalicylic acid produced significantly higher pain relief scores than the placebo ($P < 0.05$). However, the differences between any two of the drugs (excluding placebo) is not statistically significant.

TABLE I. ANALGESIC EFFECTIVENESS OF VARIOUS DRUGS USED FOR PAIN OF ALVEOLAR OSTEITIS IN 100 PATIENTS

DRUG	NUMBER OF PATIENTS	PAIN RELIEF SCORE (NUMBER OF PATIENTS)			TOTAL RELIEF SCORE	RELIEF SCORE PER PATIENT ± S.E.†
		0*	1*	2*		
Placebo	67	26	37	4	45	0.67 ± 0.07
Acetylsalicylic acid	72	24	36	12	60	0.83 ± 0.08
Dihydrocodeine	63	17	34	12	58	0.92 ± 0.09
Analgesic capsule	69	17	37	15	67	0.97 ± 0.08
Anileridine	51	13	24	14	52	1.02 ± 0.10

*See text for definition.
†Standard error of mean.

It might be expected that the intensity of pain of alveolar osteitis would decrease from the first to the fifth day of treatment. A high incidence of relief following placebo could be obtained by a disproportionately large number of placebo administrations on the later days of the study. Therefore, the pain relief scores for each drug by day of administration were determined (Table II). The scores for all drugs tended to be lower on the first day of study than on succeeding days. However, there was no consistent trend toward higher scores with days of study. The distribution of all drugs by days was fairly uniform and in accord with the experimental design.

TABLE II. NUMBER OF PATIENTS AND MEAN PAIN RELIEF SCORE FOR EACH DRUG BY DAY OF ADMINISTRATION

DRUG		DAY OF ADMINISTRATION				
		1	2	3	4	5
Placebo	No. of patients	20	20	10	6	11
	Score	0.70	0.65	0.60	0.67	0.73
Acetylsalicylic acid	No. of patients	23	19	12	12	6
	Score	0.70	1.00	0.75	0.75	1.00
Dihydrocodeine	No. of patients	17	17	13	10	6
	Score	0.88	0.94	0.92	1.00	0.83
Analgesic capsule	No. of patients	19	14	18	10	8
	Score	0.95	1.21	0.94	0.80	0.88
Anileridine	No. of patients	13	18	6	8	6
	Score	0.85	0.94	1.33	1.00	1.33

The incidence of unpleasant side effects associated with the administration of these drugs was tabulated (Table III). When the data were treated as a block, the incidence of side actions for the various drugs was significantly

TABLE III. PERCENTAGE OF PATIENTS REPORTING SIDE ACTIONS FOLLOWING DRUGS STUDIED

SIDE EFFECT	PLACEBO	ASPIRIN	DIHYDROCODEINE	ANALGESIC CAPSULE	ANILERIDINE
Sleepiness	16	6	32	23	25
Dizziness	6	10	22	4	22
Nausea	5	3	22	10	27
Vomiting	0	0	10	4	12
Drunk	0	0	3	3	0
Headache	2	0	0	0	2
Nervousness	0	0	0	1	2

different ($P < 0.03$). When differences between pairs of drugs were compared, however, no significant differences appeared because of the small number of replicates and the small differences between drugs. It is apparent, however, that the incidence of side actions following administration of placebo and aspirin was similar, as was the incidence following dihydrocodeine and anileridine. The side actions following the "analgesic capsule" were intermediate in frequency.

DISCUSSION

The occurrence of pain relief following a placebo is dependent on many factors. These factors include the personality characteristics of the patient, patient-physician relationship, environmental setting, mode of drug administration, use of suggestion, and probably others not yet recognized. The exact incidence of relief following administration of a placebo observed in any group is characteristic, therefore, of the specific group studied and the immediate therapeutic or experimental environment. Beecher,[9] in summarizing the placebo response observed by others in fifteen studies of such diverse conditions as cough, angina pectoris, seasickness, and pain, reported an average frequency of placebo relief of 35.2 per cent. This incidence is in accord with our previous experiences with parenteral analgesics in the treatment of acute postoperative pain in hospitalized patients.[10] In this study almost twice (61 per cent) the expected relief following placebo was observed in a disease known for its severe persistent pain.

A similar high incidence of relief following placebo administration was observed by Batterman and Grossman[11] in a study of antirheumatic drugs. They reported a 55 to 60 per cent incidence of pain relief by placebo given orally to outpatients for a variety of rheumatic diseases. This high incidence of relief after placebo administration might be expected because of the chronic nature of rheumatic diseases. In our study acute pain was involved, but a similar incidence of relief was obtained with a placebo. Thus, it would seem that acuteness or chronicity of symptoms was not a major determinant of relief obtained with a placebo. A more important characteristic of both these studies was the outpatient status of the subjects. It is probable that this was

a more significant determinant of relief following placebo administration, since with outpatients the investigator cannot control many environmental variables, such as social distractions, alcohol, and other therapy.

The implications of these data are obvious. In this study, which employed careful controls and experimental design, the differences between drugs known to be analgesics and a placebo were demonstrated only with difficulty because of the high incidence of relief following administration of the placebo. An attempt to draw conclusions from studies similar to this one but without these safeguards (double-blind evaluation and placebo control) would be most hazardous. The necessity for such safeguards is not limited to studies of analgesics and pain relief but applies as well to studies of drugs used to treat nausea, anxiety, sleeplessness, or, indeed, any symptom, including side effects of drugs (Table III). These safeguards are also necessary when such "objective" changes as degree of swelling, rate of healing, and amount of bleeding are subjects of study. Here the investigator's bias or "enthusiasm," in many ways more subtle and treacherous, must be controlled.

The high incidence of relief following placebo administration observed in this study indicates that careful experimental design and placebo control must be used in any study which employs outpatients or patients seen in a private office. One wonders whether any significance at all can be attached to results of uncontrolled therapeutic trials carried out in an office practice.

All drugs studied here resulted in higher pain relief scores than the placebo in the treatment of pain of alveolar osteitis. As the analgesic effectiveness of the drugs increased, however, so did the incidence of such side actions as sleepiness, dizziness, nausea, and vomiting. The high incidence of many of these side actions can be attributed to the ambulatory status of the patients, since ambulation is known to increase the side actions of narcotics.[12] The penalty of increased pain relief in these patients was increased side action liability.

SUMMARY

One hundred patients with moderate to severe pain of alveolar osteitis were treated on successive days with one to five drugs including a placebo, administered in random order. Sixty-one per cent of the sixty-seven patients who received a placebo obtained adequate relief of pain. All drugs studied produced higher pain relief scores than the placebo. As the analgesic effectiveness of the drugs increased, so did the incidence of unpleasant side actions.

The problem of the placebo response in drug evaluations was discussed briefly. The hazards of drawing conclusions from uncontrolled drug trials, especially in outpatients or office patients, were pointed out.

We are indebted to the following pharmaceutical companies for generous supplies of the drugs used in this study: Merck Sharp & Dohme, Inc., Rahway, New Jersey, supplied anileridine dihydrochloride as Leritine; Mallinckrodt Chemical Works, St. Louis, Missouri, supplied dihydrocodeine bitartrate as Parzone; Abbott Laboratories, North Chicago, Illinois, supplied the analgesic capsules.

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ETHINAMATE (VALMID) IN DENTISTRY

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THE desirability of preoperative sedation for dental procedures is generally recognized; most dentists follow a routine which involves some preliminary medication. The relaxing effect of a preoperative sedative is welcome to patient and dentist alike. In dentistry, where many procedures are performed under local or regional anesthesia, the protection afforded by the barbiturates against a possible procaine reaction has been accepted as another reason for the wide use of this group of drugs.

Although the barbiturates serve specific purposes in dentistry, many dentists have used them with certain misgivings. Even with Seconal sodium, the fastest-acting barbiturate, the effects are not immediately detectable and definitive therapy may, therefore, be delayed. Furthermore, the incoordination and confusion which often follow barbiturate sedation are undesirable in ambulatory patients. In addition, many practitioners hesitate to use a drug which might be habit-forming.

The ideal preoperative medicament for an ambulatory dental patient would have the following attributes: (1) nontoxic, (2) nonhabit-forming, (3) rapid onset of sedation after oral administration, (4) very short duration of effect, (5) freedom from lingering after effect, (6) no medical contraindications, and (7) protection against procaine toxicity.

Pharmacologic and clinical studies indicate that a new hypnotic, ethinamate,† should fulfill the requirements outlined above.

PHARMACOLOGY

Ethinamate is an effective sedative-hypnotic with a rapid onset and a very brief span of action. It is a unique chemical compound, unrelated to barbituric acid and unlike any other sedative-hypnotic currently available. Ethinamate is an odorless, colorless, faintly bitter, stable, crystalline powder.[1] In man it rapidly produces central nervous system depression. Of all the available oral hypnotics, ethinamate has the shortest duration of action. No evidence of damage to any organ or system has been observed following the

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use of ethinamate. There are no known contraindications to its use. Ethinamate, in usual doses, has no specific effect on blood pressure, pulse, or respiration.[1, 2] In laboratory animals ethinamate has been shown to protect against procaine toxicity to a degree equal to that of the barbiturates.[3]

It is apparent that ethinamate should be useful in dentistry, and theoretically, by its use, the undesirable clinical features of the currently used drugs should be avoided. Accordingly, a clinical investigation of the compound was carried out at Indiana University School of Dentistry.

METHOD

Tablets of 500 mg. of ethinamate and placebo, identical in appearance, were used in this study. A tablet of one of these preparations was administered orally in random order to unselected adult patients twenty to thirty minutes prior to oral surgery. The double-blind technique was used. The patient was observed during this initial period and then questioned as to what effect, if any, the medication had produced. Both the patient's subjective response and the investigator's objective evaluation were recorded. The investigator based his opinion on the apparent degree of relaxation of the patient, regardless of the patient's subjective response. The following categories were used in evaluating the medication: (a) of definite help, (b) of questionable help, and (c) of no help at all.

RESULTS

As seen in Table I, most of the patients receiving ethinamate felt that it was of definite help, while very few of those receiving the placebo felt that it was of value. Few thought that ethinamate was of no benefit, while nearly one-half placed the placebo in that category. This distribution of responses would not be expected to occur by chance.

TABLE I. THE PATIENTS' EVALUATIONS

MEDICATION	DEFINITE HELP	QUESTIONABLE HELP	NO HELP	TOTAL
Ethinamate	99	5	10	114
Placebo	8	50	40	98
Totals	107	55	50	212

Table II reports the investigators' evaluations. These results are very similar to those reported in Table I. Both sets of data indicate that this evidence of the superiority of ethinamate over placebo would not be expected to occur by chance. No side effects were noticeable with either ethinamate or the placebo while the patients remained in the clinic.

TABLE II. THE INVESTIGATORS' EVALUATIONS

MEDICATION	DEFINITE HELP	QUESTIONABLE HELP	NO HELP	TOTAL
Ethinamate	91	7	16	114
Placebo	4	29	65	98
Totals	95	36	81	212

CONCLUSION

Ethinamate, a new nonbarbiturate compound, is very satisfactory for preoperative medication of dental patients undergoing oral surgical procedures. It produces sedation in a relatively short period; no lingering side effects were observed.

SUMMARY

A double-blind study with ethinamate and a placebo was performed, with 114 patients receiving ethinamate and 98 receiving placebo. Ethinamate was judged by both operators and patients to be of definite value. The dosage of ethinamate used in the study was one tablet, 500 mg.

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ANESTHESIOLOGY

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METHITURAL SODIUM (NERAVAL SODIUM), AN INTRAVENOUS ANESTHETIC FOR ORAL SURGERY PROCEDURES

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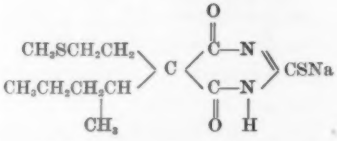
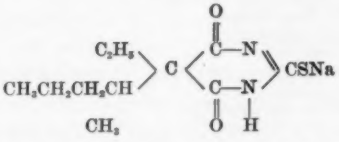
METHITURAL sodium (Neraval sodium) is one of the many short-acting thiobarbiturates, which differs chemically from thiopental sodium in that it has an additional methylthioethyl radical. Its chemical formula may be compared to thiopental sodium and studied from the standpoint of structural formulas:

Methitural Sodium



Thiopental Sodium



This compound was first synthesized and tested[1] with the expectation that this particular barbiturate molecule would undergo degradation and detoxification more rapidly, affording a shorter recovery period and less accumulative effect; however, it is thought that the shorter action of methitural sodium is due to its greater fat solubility.[2]

It has been claimed that methitural sodium demonstrates clinical advantages over the other thiobarbiturates when used as the sole anesthetic agent for short dental procedures. These advantages are listed as less cumulative effect, faster elimination of the drug, lower potency, less respiratory depression, less cardiac acceleration, and more rapid recovery.[3, 4] More important than new anesthetic agents available to the dental profession is the thorough knowledge of the principles of anesthesia and the complications which one expects to encounter.

The purpose of this article is to summarize the clinical advantages and disadvantages of methitural sodium as an anesthetic agent, with particular

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concern for the ambulatory patient. For the sake of brevity, no attempt will be made here to present the pharmacology, as this material may be found in other reports.[4] We wish to emphasize, however, that in interpreting clinical findings one must be cognizant of the established pharmacologic knowledge of the drug.[4-7]

For many years before the introduction of methitural sodium, thiopental sodium had been widely used as an anesthetic agent of choice in oral surgery offices. Therefore, in attempting to evaluate methitural sodium clinically, we shall include comparative notes on thiopental sodium as the established standard.

In the oral surgery clinic in which our studies were carried out, thiopental sodium was used as the general anesthetic agent for short dental operations.* A 2 per cent solution was used with a syringe technique, and in the average case it was supplemented with 75 per cent nitrous oxide and 25 per cent oxygen. On the initial induction dose 0.4 mg. of atropine was given. No other premedication was used.

TABLE I. THIOPENTAL SODIUM WITH NITROUS OXIDE-OXYGEN SUPPLEMENTATION (THIRTY-FIVE CASES)

1. Average weight	146 pounds—66.2 Kg.
2. Average length of anesthesia	18.7 minutes
3. Average amount of thiopental sodium	638 mg.
4. Average per kilogram per minute thiopental sodium	0.6 mg.
5. Waking time	15-45 minutes
6. Laryngospasm	2
7. Hiccups	2
8. Cough	0
9. Tremors	1
10. Alert on awaking	0

A control group of thirty-five cases in which thiopental sodium was administered was observed (Table I). Ages ranged from 14 to 65 years, and the average weight was 146 pounds. Anesthesia time averaged 18.7 minutes. The average dose of thiopental sodium was 0.6 gram (638 mg.). In order to standardize and compare the amount of barbiturate used in one case with the amount another used, we have reduced our figures to milligrams of anesthetic agent per kilogram of weight per minute of anesthesia duration. In these thirty-five cases the per kilogram per minute of thiopental sodium averaged 0.6 mg.

Our figures on waking time were not complete; therefore, we are including an estimate made by the nurse who has been in charge of anesthesia at the oral surgery clinic for the past twenty years. She estimates that the average waking time following oral surgery procedures (when the patient demonstrates no vertigo and is aware of his surroundings) is forty-five minutes.

*We are indebted to the Miller Oral Surgery Clinic in Harrisburg, Pennsylvania, for their cooperation in compiling data on thiopental sodium and methitural sodium as the anesthetic agents during dental procedures.

METHITURAL SODIUM STUDY

A study of seventy-five cases in which a 2.5 per cent solution of methitural sodium (Neraval sodium) was used as the anesthetic agent was conducted at the oral surgery clinic (Table II). The patients ranged in age from 17 to 65 years, and the average weight was 142 pounds. An average of 0.8 gram (802 mg.) of methitural sodium was given, and the length of anesthesia averaged 8.7 minutes. The average per kilogram per minute of methitural was 2.17 mg. Waking time ranged from the conclusion of operation to thirty-three minutes, with an average of eight minutes. However, one must note that the length of anesthesia for this group is one-half that for the previous thiopental sodium group, and the waking time may be expected to vary.

TABLE II. METHITURAL SODIUM WITH NITROUS OXIDE-OXYGEN SUPPLEMENTATION (SEVENTY-FIVE CASES)

1. Average weight	142 pounds—64.7 Kg.
2. Average length of anesthesia	8.7 minutes
3. Average amount of methitural sodium	802 mg.
4. Average per kilogram per minute methitural sodium	2.17 mg.
5. Waking time	8-33 minutes
6. Laryngospasm	3
7. Hiccups	10
8. Cough	14
9. Tremors	1
10. Alert on awaking	2

At the Harrisburg Hospital a group of fifty-eight cases in which methitural sodium was used was studied. This consisted of a 1 per cent drip technique in a double-blind study against a 0.5 per cent solution of thiopental sodium. A 0.1 per cent drip of succinylcholine was used intermittently during the operation for muscle relaxation, in addition to nitrous oxide-oxygen supplementation. During this comparative study of methitural sodium and thiopental sodium the anesthetists administering the agents were unaware of which barbiturate the anesthesiologist had placed in the operating room. It was thought that from such a blind study the nurse anesthetists might chart their observations uninfluenced by previous impressions and opinions that might have been gathered from literature and experience.

It soon became quite obvious to the nurse anesthetists who were unknowingly using methitural sodium that the induction time was prolonged, even with the difference in percentage of solutions used. It was also obvious that the total number of grams given to maintain light planes of anesthesia was greater.

With the use of a 0.1 per cent succinylcholine drip and nitrous oxide-oxygen supplementation, it is the opinion of those who are administering general anesthesia at Harrisburg Hospital that the two barbiturates used in this study demonstrated no difference in reflex and waking time. With this technique, it was also difficult to observe any differences in the side reactions supposedly demonstrable in the two drugs. These hospital control groups were carried out and charted, and the analysis and summary are presented

in this article for the purpose of demonstrating that only when methitural sodium is used as the sole anesthetic agent will one observe a noticeable difference in waking time. These hospital patients received routine atropine and scopolamine premedication.

RESULTS

In the oral surgery clinic, methitural sodium in a 2.5 per cent solution was given to seventy-five patients as the primary anesthetic agent, supplemented with 75 per cent nitrous oxide and 25 per cent oxygen. No preoperative medication was administered; however, $\frac{1}{150}$ gr. of atropine was given with the initial dose. Recovery was rapid and complete, so that the patients were able to go home within thirty to forty minutes.

Methitural sodium was given to fifty-eight surgical patients undergoing various types of procedures at the Harrisburg Hospital. Methitural sodium was used as the induction agent, supplemented with nitrous oxide and oxygen, and light planes of anesthesia were maintained by intermittent drip administration of 1 per cent methitural sodium and 0.1 per cent succinylcholine. These patients required a greater amount for induction and more frequent subsequent administrations to maintain light planes of anesthesia than did patients given thiopental sodium by this technique.

Complications.—During induction with a 2.5 per cent solution of methitural sodium at the oral surgery clinic, patients frequently coughed and demonstrated transient hiccups. Such complications were not noticed when a 1 per cent drip was used at Harrisburg Hospital. No differences in the incidence of laryngospasms, blood pressure changes, cardiac rate, and respiratory amplitude and frequency were noted in this short study.

SUMMARY

Methitural sodium, a new short-acting thiobarbiturate anesthetic favorable for use in the oral surgery office as an intravenous anesthetic, demonstrates some noticeable advantages in that it shows a lessened recovery time with more complete mental alertness upon recovery. Side effects observed in this short study of only seventy-five cases are not conclusive in view of the fact that such complications as laryngospasms may be produced irrespective of the type of anesthetic used.

Since it is our opinion that all short-acting thiobarbiturates being used today can be direct myocardial and respiratory depressants,[2] methitural sodium (Neraval sodium) offers among its advantages a slower induction, which is desirable in view of these facts, and the patient awakes faster, which is an advantage in resuscitating the depressed patient.

Since the advent and employment of muscle relaxants, surgery is performed in very light planes of anesthesia. In the dental office the routine use of muscle relaxants as an anesthetic adjunct is not practical due to the fact

that controlled respiration is somewhat disadvantageous to the operator. Because of the high fat-solubility ratio of methitural sodium, the continuous administration of methitural sodium enables the operator to maintain a light plane of anesthesia with less chance of rapidly overdosing the patient.

Methitural sodium seems to be a safe anesthetic agent for dental procedures when administered by qualified and experienced anesthetists. As experience is gained over the years, we will become more familiar with all the advantages and disadvantages of the short-acting thiobarbiturates. As no one antibiotic is sufficient for all infections, no one anesthetic agent will be the panacea for all anesthesia needs.

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ORAL PATHOLOGY

BIOPSY PROCEDURES

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IT CAN be said, and no doubt has been said, of the oral pathologist that all he has to learn is the art of writing reports that "hedge" in such a manner that, no matter what the final diagnosis is, the report appears to fit. If there is a grain of truth in the preceding fatuous statement, it rests on the fact that many biopsy specimens may be useless for an adequate histologic interpretation.

I wish to emphasize the fact that, if a patient is to receive the maximum benefit from the oral surgeon and the oral pathologist in the diagnosis of any given lesion, a good biopsy specimen is essential. It is not easy to procure a good biopsy specimen, nor is it very difficult, but the procedure must be carefully planned and expeditiously carried out, and the provisional diagnosis must be borne in mind.

The person performing this minor surgical technique must be familiar with oral pathology and preferably should be working in close cooperation with, if not within, a pathology department, so that he may study a section of the material removed. That is not to say that one cannot perform biopsies outside hospitals; of course one can, and many do, requesting a slide for study with the report. In fact, oral pathology departments are always pleased to report on material from these sources. Nevertheless, in the patient's best interests, when malignancy is suspected, the patient should be referred directly to the specialist.

The histologic diagnosis, invaluable though it may be, is only an important link in forming a definitive diagnosis. The latter is arrived at only after the history, clinical features, radiographic appearances, and in some cases the serum investigations have been weighed together with the microscopic picture. More often than not the biopsy is the last link in the diagnostic chain, and it is very important that all the other evidence is presented with the specimen to the pathologist, if the latter is to be of the greatest possible assistance.

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Part of the papers read before the monthly conference of the New York Institute of Clinical Oral Pathology, March 25, and the Course in Clinical Oral Pathology, March 27, 1957.

While a positive histologic diagnosis that agrees with the provisional clinical diagnosis is very satisfying to all concerned, it may happen that the respective diagnoses are, in fact, quite different. It is in the latter case that the clinician and pathologist should talk the case over together, each giving the reasons for his point of view. This is not only to the patient's advantage but is instructive to the clinician and pathologist concerned, more so than spending many hours consulting books. More will be said about this in the discussion of case management of a suspected carcinoma.

Since biopsy procedures vary according to the provisional clinical diagnosis, the site, and whether soft or hard tissue is involved, they will be discussed along with representative diseases.

CARCINOMA

I am in full agreement with Boyle,[1, 2] who wrote, in 1954, that the only acceptable diagnosis of malignant disease, particularly in the early stage is a microscopical one and, again in 1955, that "the taking of a biopsy when the clinical impression is squamous-cell carcinoma should be performed by a specialist who, by training and experience, is best qualified to do so, and who will assume responsibility for the treatment."

An often repeated statement that if a suspicious-looking chronic ulcer does not show signs of healing within a fortnight after institution of treatment malignancy should be suspected and a biopsy performed is quite indefensible, for failure to perform a biopsy when the ulcer is first seen wastes a fortnight.

Theoretical arguments have often been raised concerning the risk of metastases following a biopsy, but in practice this is seldom encountered. It is imperative that a microscopic diagnosis be made if extensive operations are to be avoided for tumors which are not, in fact, malignant. On the other hand, repeated biopsies must be done in the case of lesions which on clinical grounds are suspected of being carcinomas, but which histologically cannot be shown to be so. Fig. 1 shows the palate of a 66-year-old man in whom the diagnosis of a carcinoma was made only after four biopsies.

While it is imperative that a biopsy be carried out, gentleness must be observed at all times. Fig. 2 shows a carcinoma of the gingiva with malignant epithelial cells lining a blood vessel. The local anesthetic must be given well away from the tumor, and the site for biopsy must be carefully chosen. In the majority of cases the margin of the normal and the abnormal is suitable, for it helps in the orientation of the specimen and avoids necrotic areas in the center. Unfortunately, the carcinoma interferes with the nutrition of surrounding epithelium and the latter may appear neoplastic; thus, unless one is careful to make a long enough incision into the tumor, the malignant cells may be missed. Minute specimens are just as difficult (if not more so) to remove as adequate ones approximately 1 cm. long, 0.5 cm. wide, and 0.5 cm. thick. Incisions that appear to give large specimens in the mouth often produce disappointingly small specimens in the bottle of 4 per cent formalin and even smaller sections on the slide. Care should be taken not to penetrate the underlying periosteum if the carcinoma covers bone.

As in the technique to be described for obtaining a biopsy specimen from a patch of leukoplakia, the tissue must not be crushed by forceps. When the growth is extensive, an anesthetic may not be needed, or a surface anesthetic will suffice. Bleeding or postoperative discomfort is minimal after biopsy of a carcinoma.

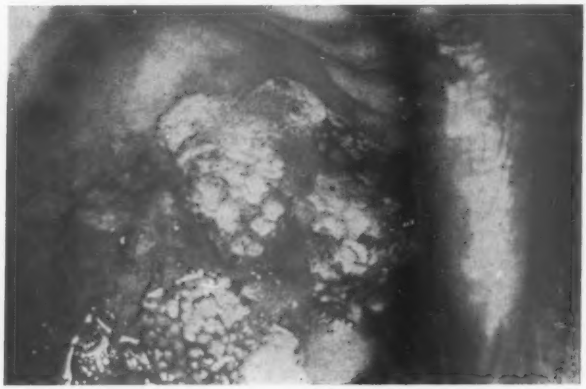


Fig. 1.—Squamous-cell carcinoma of the palate of a 66-year-old man.

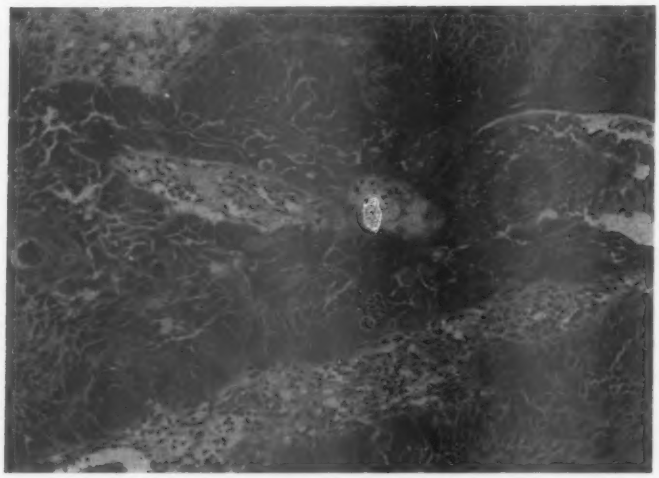


Fig. 2.—Anaplastic squamous-cell carcinoma of gingiva showing neoplastic epithelial cells lining a blood vessel. (Hematoxylin and eosin stain. Magnification, ×120.)

If the pathologist himself did not perform the biopsy, the clinical notes accompanying the specimen must include a drawing outlining the lesion and the exact spot from which the material was taken. The value of a simple line drawing cannot be overemphasized. The pathologist's report will be made

within twenty-four hours, and within eight hours if necessary, so that if the diagnosis of carcinoma is confirmed consultation can begin between the surgeon and the radiotherapist and the appropriate treatment can be begun without delay.

I am not happy about epithelial smears for the diagnosis of oral carcinoma. Pomeranz and Stahl,[7] in a correlative study of cytodiagnosis and biopsy, thought that although they should not be relied upon alone, they were an adjunct to the biopsy technique. In four cases, a diagnosis of carcinoma was made earlier than with a biopsy, possibly because the smears covered a greater area than a biopsy. Perhaps the true nature of the case illustrated in Fig. 1 would have been diagnosed earlier if epithelial smears had been obtained.

The punch biopsy has only a limited place in lesions of the oropharynx that are difficult of access by normal methods without a general anesthetic. The ear, nose, and throat surgeon is experienced in this technique for lesions posterior to the anterior pillar of the fauces.

WHITE PATCHES

A white patch on the oral mucosa often reflects abnormalities of keratinization following friction, smoking, syphilis, developmental anomalies, and the confluent papular pattern of lichen planus. A biopsy may be desirable to help distinguish one of these lesions from the other and to detect any possible precancerous features.

The occlusal line of the cheeks is best avoided in biopsies of lichen planus, for here the microscopic picture may be modified by a mild frictional keratosis.

In choosing the part of a patch of leukoplakia to be biopsied for possible malignant change, it is not always the margin or even the most thickly keratinized part that should be chosen. Since a prickle cell can either form keratin or divide, and it cannot do both at the same time, the part which is likely to show the most advanced precancerous change is any area that rather resembles granulation tissue, and may only be flecked with keratin. Small patches are better removed in their entirety.

I have described the following technique[13] which is applicable to many lesions of the oral mucosa, such as leukoplakia, lichen planus, lupus erythematosus, etc. The aim of this technique is to avoid the slightest trauma to the specimen during its removal, which will render any histologic findings (such as early bulla formation) subject to suspicion.

The lesion removed is untouched by forceps, and every attempt is made to obtain a specimen of even thickness throughout, thus avoiding shallow and wedge-shaped fragments.

This technique, illustrated in the accompanying diagrams, is carried out under local anesthesia (2 per cent procaine and 1:50,000 epinephrine). No antiseptics are applied prior to the biopsy.

The local anesthetic is given with a short needle (1 inch, 21 gauge) away from the site of the lesion to be examined, so as to reduce any risk of artifact,

and then the first incision is made with a No. 11 Paragon blade (Fig. 3, *A*). This blade is especially useful, for it cuts on its point and is well designed for the next step of undermining the mucosa to the required depth (Fig. 3, *B*). The

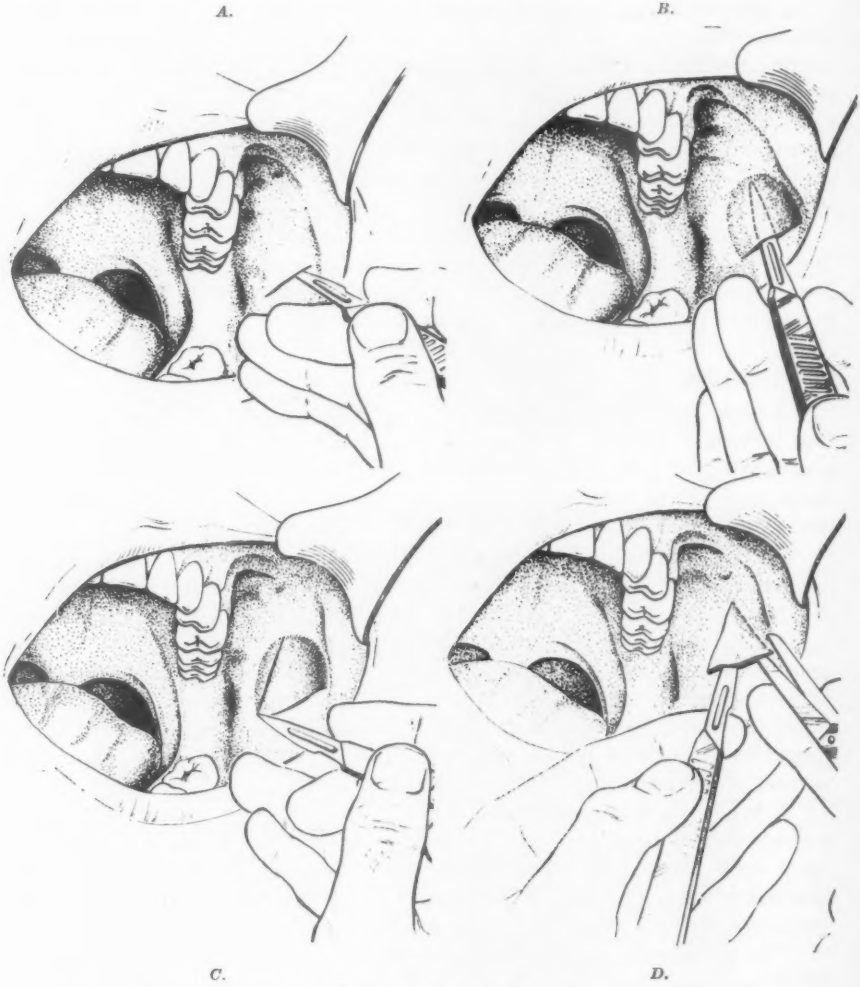


Fig. 3.—(From Cooke, B. E. D.: *Brit. J. Dermat.* **68**: 151, 1956.)

next stage is another incision, completing two sides of a triangle (Fig. 3, *C*), after which the biopsy specimen can be lifted off its bed with the point of the blade and finally cut free with scissors (Fig. 3, *D*) and placed directly into 4 per cent formalin. If the specimen has a tendency to curl, it is first placed on a piece of blotting paper, after which it will retain its form in the fixing fluid.

One black silk suture is all that is necessary to close the incision and arrest any hemorrhage. Healing is uneventful and the patient suffers no more discomfort than if he had bitten his cheek. The stitch is removed after two days.

EPITHELIAL NEVI OF THE ORAL MUCOSA

This very important clinical entity has to be distinguished from other lesions featuring abnormal keratinization. Congenital anomalies of the mucous membrane have not received the same attention as those of the skin, as a result of the tendency to class all white patches on the mucosa as leukoplakia. Occasionally, in the dermatologic literature, reference has been made to the association of anomalies of the oral mucosa with disorders of keratinization of the skin, as in patients suffering from generalized ichthyosis, pachyonychia congenita, dyskeratosis congenita palmaris and plantaris, and dystrophia corneae. In 1956 I reviewed the literature of this condition and described six further cases.[3]

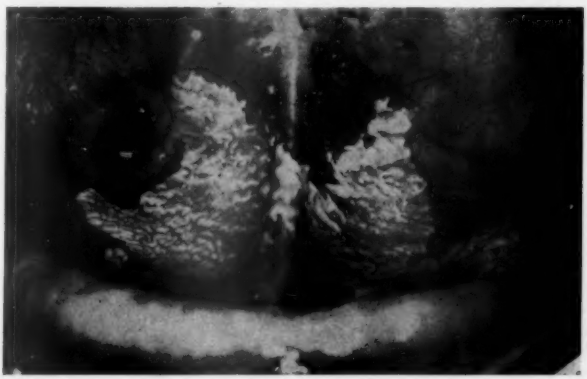


Fig. 4.—Epithelial nevus on the ventral surface of the tongue and spreading anteriorly on to the floor of the mouth in a 39-year-old woman. (From Cooke, B. E. D.: *Brit. J. Dermat.* 68: 151, 1956.)

An oral epithelial nevus may be discovered in either male or female patients at any age, for, being symptomless, it may remain unnoticed by the patient. It can be present at birth or it may develop later in life. A family history is sometimes obtained. Generally no other abnormality of the skin is discovered in the patients affected.

The lingual sulcus in the floor of the mouth and the attached gingivae lingual to the lower incisors appears to be a favorite site, but any part of the oral mucosa may be involved. In some cases there is an appearance of symmetry (Fig. 4).

The affected area is dense white, well defined, and raised above the level of the surrounding mucosa. The latter is normal in appearance. The white patch has a regular wrinkled appearance without tessellation or wartiness on

Fig. 5.

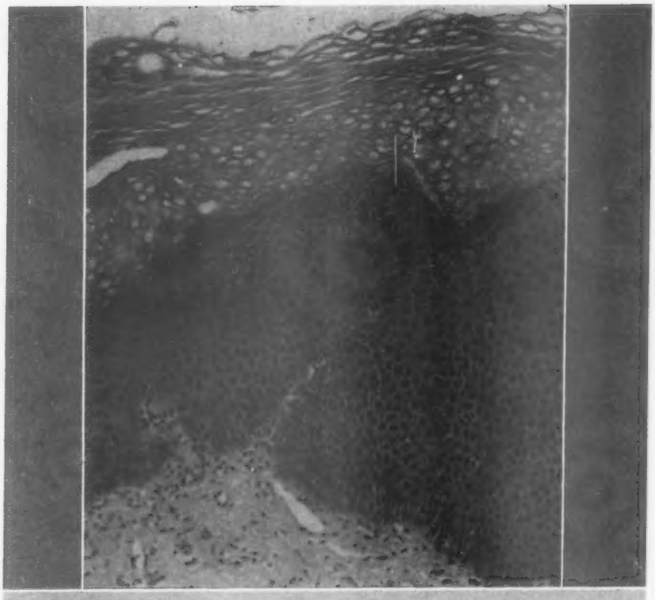


Fig. 6.

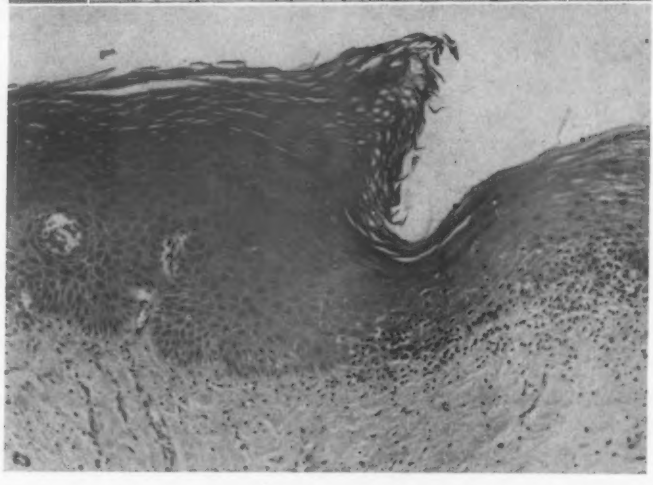


Fig. 5.—Epithelial nevus on the floor of the mouth featuring a basket-weave appearance of the thick keratin layer, acanthosis, and a thick granular layer. There is no infiltration of the underlying corium. (Hematoxylin and eosin stain. Magnification, ×120.) (From Cooke, B. E. D.: *Brit. J. Dermat.* **68**: 151, 1956.)

Fig. 6.—Epithelial nevus on the floor of the mouth featuring the well-defined margin of the affected area to the normal nonkeratinized mucosa. (Hematoxylin and eosin stain. Magnification, ×120.)

the floor of the mouth and on the gingiva. On the floor of the mouth and on the ventral surface of the tongue it resembles the undulations left in the sand by an ebbing tide, quite different from leukoplakia, which is more like paint cracking in the sun.

Histopathology.—From a study of two biopsy specimens taken from the lingual sulcus, which when normal is not keratinized, there appear to be two main abnormalities: (1) the keratinization of a normally nonkeratinized mucosa and (2) an increased rate in the production of keratin as shown by the very thick layer of keratin, by acanthosis, and by an unusually thick granular layer. In places the keratin has a definite basket-weave appearance (Fig. 5). There is no abnormality of the underlying corium, and the margin of the affected area to the normal nonkeratinized mucosa is well defined (Fig. 6).

GINGIVAL BIOPSIES FOR AMYLOID

In my experience, this is the most unrewarding biopsy to perform. Usually the patient has a negative Congo red test and equivocal physical signs, and amyloidosis is the hoped for diagnosis. Selikoff and Robitzek[8] reported that, in a series of forty-seven patients with negative Congo red tests, eighteen had positive physical signs and, of these, fourteen showed amyloid in the gingiva. There was no correlation between the amount in the gingivae and that in the viscera. Selikoff and Robitzek advised fixing the gingiva in alcohol, staining with methyl violet, and looking for metachromasia by diffuse sunlight. This has led general physicians and dermatologists to request gingival biopsies, but my experience agrees with that of Symmers[8] of Charing Cross Hospital, namely, that the blind biopsy of clinically normal tissue is often unrewarding and so far has been 100 per cent unsuccessful. It is, of course, not known whether any of the patients biopsied in this way have amyloidosis, and a control series of known cases will have to be examined. Symmers says that in the tongue, if amyloid is present, a properly done biopsy will heal slowly.

GINGIVAL BIOPSIES IN VINCENT'S DISEASE

Working in close liaison with Mr. Ronald Emslie, I have taken twenty biopsy specimens in this condition, and in none could any organisms be found in the living tissues.

GINGIVAL BIOPSIES IN SUSPECTED BLOOD DYSCRASIAS

Any sort of biopsy is, of course, contraindicated in patients thought to be suffering from a blood dyscrasia. Smears of the peripheral blood stream must be made first. Tissue fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin is useless for identifying a leukemia and only adds to the patient's distress.

MIXED SALIVARY TUMORS

The clinical diagnosis is often so clear cut that a biopsy is rarely needed before the tumor is operated upon. Nevertheless, there are cases in elderly

persons who are not operated upon, and a biopsy may be indicated in order to make sure of the diagnosis and to exclude an adenocystic carcinoma. Salman and Langel[6] do not advise biopsy of a mixed salivary tumor for fear of disturbing the capsule. This approach is difficult to understand, for the tumor is slow growing and, besides, the capsule is disturbed on the superficial aspect and not the deep one. Anyway, the epithelial cells infiltrate the capsule without the help of a scalpel.

CYSTS AND SUSPECTED ADAMANTINOMAS

Aspiration of the contents of a cyst before operation will avoid the occasional error of trying to treat a solid lesion, such as a reparative granuloma of bone, as a cyst. The discovery of abundant cholesterol crystals will exclude an adamantinoma.

There is no proof that an adamantinoma has ever arisen from the lining of a periodontal or dentigerous cyst, unless all the lining of the original cyst has been serially sectioned and the pathologist concerned is fully familiar with the wide range of epithelial hyperplasia that may mimic neoplasia.

Since the current treatment for an adamantinoma is to remove the tumor together with ½ inch of adjacent normal bone, breaking if necessary the continuity of the jaw, it is imperative that a histologic preoperative diagnosis be made to avoid extensive operations on lesions with similar radiographic appearances, such as primordial cysts. While, on exceptional occasions, a drill biopsy may succeed, it is not the desirable approach, for it is better to reflect the overlying mucosa, remove a section of the lining, and then suture the mucosa carefully back into place. This method allows the cyst to be explored and avoids secondary infection. If an adamantinoma is marsupialized by mistake for a dental cyst, there may be secondary hemorrhage.

USE OF THE BIOPSY DRILL IN THE DIAGNOSIS OF FIBRO-OSSEOUS ENLARGEMENTS OF THE JAWS

Whereas many fibro-osseous enlargements of the jaws do not require any surgical treatment, it is desirable to obtain a biopsy specimen, if only to confirm a provisional clinical and radiographic diagnosis. The biopsy drill designed by Ellis[4] for obtaining specimens from deep-seated lesions in the body was adapted and successfully used by Miles[5] to diagnose central lesions of the jaws. The drill consists of a hollow steel tube with the same outside diameter as a dental burr, thus fitting a straight dental handpiece (Fig. 7). The cutting edge of the drill consists of two pointed teeth, and specimens are produced 1 to 2 cm. in length and about 1.4 mm. in diameter. This cutting edge has been found to be the most satisfactory for fibro-osseous lesions and, with care in embedding and sectioning, about 100 sections may be obtained from one specimen.

Advantages of the biopsy drill:

1. With experience, it is an easy and safe way of obtaining biopsy material from central fibro-osseous lesions in the jaws.

2. The biopsy is performed under local anesthesia and is therefore an outpatient procedure.

3. It provides a specimen in depth, which is just what is needed for studying the natural history of bone dystrophies (Fig. 8).

4. The hole made by the drill is so small that infection from the mouth is unlikely to reach the bone.

5. Since it causes so little discomfort to the patient, it may be used for serial biopsies at intervals of a few years.

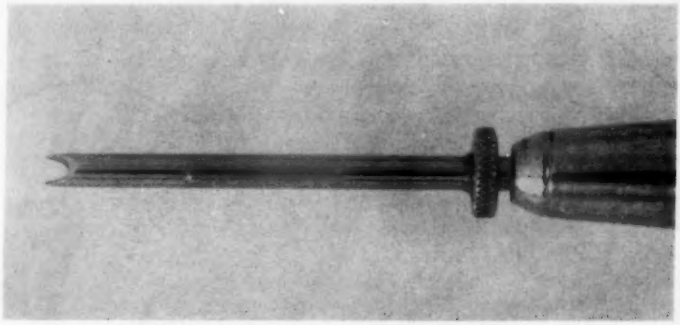


Fig. 7.—The biopsy drill attached to a straight dental handpiece.

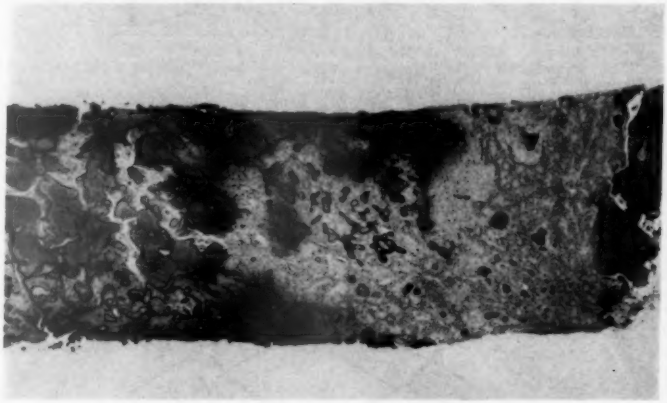


Fig. 8.—Drill biopsy specimen of an ossifying fibroma in the mandible of a 52-year-old man. (Hematoxylin and eosin stain. Magnification, ×14.)

Disadvantages of the biopsy drill:

1. The biopsy fragment is so small that it may not be representative of the whole lesion, but more than one biopsy may be taken at different sites.

2. There is sometimes distortion of the fragment from heat generated by the drill cutting the bone, but with care this can be avoided and is minimal in the fibro-osseous lesions.

SURGICAL SPECIMENS

Many other specimens examined in an oral pathology department are surgical specimens removed at operation. These, too, are sometimes damaged by toothed forceps and Spencer Wells's forceps (Fig. 9). Fig. 10 illustrates a method for removing a polyp from the oral mucosa with a stitch rather than with forceps. If bleeding is expected, as on the tongue, it is a wise precaution to have stitches in place before the specimen is removed (Fig. 11).

Fig. 9.

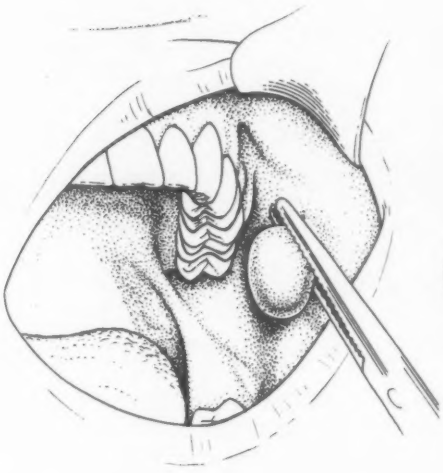
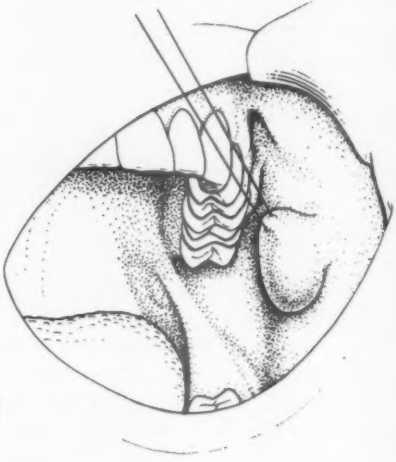


Fig. 10.



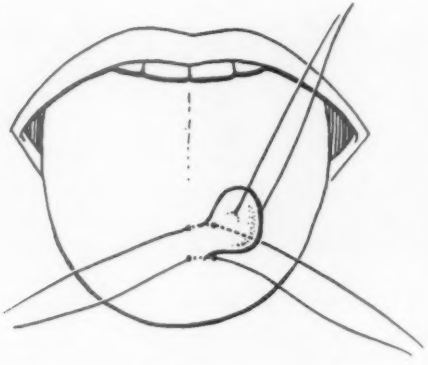


Fig. 11.

If possible, surgeons should resist the temptation to cut a specimen in half. If they do cut it in half, however, they should describe the consistency of the lesion and the appearance of the cut surface. Unfortunately, the plane chosen by the surgeon to cut the specimen is not always the one that the

pathologist would choose to obtain the best histologic section. For example, it is important to cut across the narrowest margin of normal tissue in order to be sure that the lesion has been completely removed.

A provisional diagnosis should always accompany the specimen, if only because the possibility of a carcinoma will mean that the report will be given priority. If a slide of the specimen is desired as well as the report, it should be asked for at the time the specimen is submitted; otherwise, if the paraffin block has to be set up again, valuable material is wasted in cutting another section.

Finally, the value of a specimen for display purposes in a museum should always be borne in mind. It is wise to have some Kaiserling I solution available, so that the color of any specimen will be retained. The specimen will still need further treatment with other Kaiserling solutions, so that it should reach the pathology department within twenty-four hours.

This study has been carried out in the Department of Dental Medicine, Guy's Hospital (Director, Professor M. A. Rushton, M.D., F.D.S.). I wish to thank Professor Rushton for permission to submit this paper and all the consultant staff of Guy's Hospital Dental School for awarding me a travel grant that has enabled me to visit the United States of America.

Finally, may I say how grateful I am to the Department of Dental Photography and to Mr. J. E. Hutchinson for the photographs and photomicrographs which illustrate the paper.

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ADENOAMELOBLASTOMA

Robert J. Gorlin, D.D.S., M.S., and Anand P. Chaudhry, B.D.S., Ph.D., Minneapolis, Minn.

DURING the past ten years, reports of sixteen cases of what has been called "adenoameloblastoma" have been published. Two new cases are reported here. The lesion was first recognized as a distinct entity in 1948 by Stafne,[1] who called it an epithelial tumor "associated with developmental cysts of the maxilla." It was soon shown that this tumor is not restricted to the maxilla, for Miles[2] reported this same lesion as a "cystic complex composite odontome" in the mandible of an 18-year-old boy. The other cases have been reported by Thoma,[3] Oehlers,[4] Bernier and Tiecke,[5, 6] and Lucas.[7] From Table I we can see that the tumor occurs twice as commonly in females (6 males to 12 females), that it occurs about as commonly in either jaw, and that, with but few exceptions, it is found in the second decade (10 to 20 years) of life. Radiographically, the tumor is quite frequently radiolucent. Although some degree of calcification is usually found microscopically, it seldom is sufficient to produce increased radiographic density. It is frequently, but by no means constantly, associated with unerupted teeth. Neither is it always found in the lateral incisor-cuspid-premolar region, although the majority of cases have occurred in this area. There appears to be uniform opinion that recurrences do not occur and that, although the lesion may expand, the process appears to be rather slow. The cases reported by Aisenberg[11] have not been included in this survey because of lack of his clinical data. The second of his cases of hemangioameloblastoma seems to be compatible with the diagnosis of adenoameloblastoma.

The origin of the tumor is a matter of considerable doubt. Several theories have been offered, none of which is completely satisfactory. Stafne suggested the possible origin from enclaved epithelial rests resulting from fusion of the globular and maxillary processes, but this does not hold true for several other cases in which no embryonal fusion occurred at the site of tumor origin. Salivary gland origin was suggested by Willis (per Oehlers), but this tumor has never been seen in either major or minor salivary glands.

Perhaps the choice of name is rather unfortunate, as one may draw erroneous conclusions concerning its probable clinical behavior. In no way does its clinical course resemble ameloblastoma (Table II). It expands but is not

From the Division of Oral Pathology, School of Dentistry, University of Minnesota.

locally invasive. Simple excision (it nearly always shells out quite easily!) apparently assures a "cure." Microscopically, there is a certain degree of resemblance to ameloblastoma, but the cell of the adenoameloblastoma has its nuclei basally polarized while the opposite is true in the case of the ameloblas-

TABLE I. ADENOAMELOBLASTOMA

AUTHOR	SEX	RACE	AGE	LOCATION	RADIOGRAPHIC
Stafne (1948)	M	W	15	Maxilla	Radiopaque
	F	W	16	Maxilla	Radiopaque
	F	W	14	Maxilla	Radiolucent
Miles (1951)	M	W	18	Mandible	Radiolucent
Thoma (1955)	F	W	11	Mandible	Radiolucent
Bernier and Tiecke (1956)	M	W	13	Mandible	Radiolucent
	F	W	13	Maxilla	---† ---
	F	W	26	Mandible	Radiopaque
	M	W	14	Mandible	Radiolucent
	M	M	17	Maxilla	Radiolucent
	M	N	43	Mandible	Radiolucent
	F	W	21	Maxilla	Radiolucent
	F	N	20	Mandible	Radiolucent
	F	W	11	Mandible	Radiolucent
Oehlers (1956)	F	M	15	Maxilla	Radiolucent
Lucas (1957)	F	W	19	Maxilla	Radiopaque
Gorlin and Chaudhry*	F	W	18	Maxilla	Radiolucent
	F	W	13	Maxilla	Radiolucent
Total	6 Male 12 Female	14 White 2 Negro 2 Mongolian	18 years (average)	10 Maxilla 8 Mandible	4 Radiopaque 13 Radiolucent 1 Unknown

*Since this article was submitted, a review of our files has yielded another case in a 16-year-old white girl. This case was unique in being extraosseous. It had been present for three years in the maxillary central lateral gingiva. No recurrence was noted over a twelve-year follow-up.

TABLE II

	AMELOBLASTOMA	ADENOAMELOBLASTOMA
Age (years)	30-35	11-21
Sex	Males, predominantly	Females, 2:1
Location	Mandible—ramus, angle molar region	Most in anterior region of jaws
Behavior	Recurrence common; removal sometimes very difficult	No recurrences; removal easy—tumor shells out; commonly associated with impacted tooth
Histology	Follicle-like structures formed, which frequently contain stellate reticulum	Numerous tubules, some of which are patent; some contain debris or eosinophilic material in lumen next to lining cells; no stellate reticulum
	Rarely has calcified structures except craniopharyngioma	Commonly exhibits calcified spherical bodies
	Nuclei of cells lining follicles are polarized toward lumen	Nuclei of cells lining "tubules" are polarized away from lumen
	No elaboration of hyaline eosinophilic lumen lining	Common elaboration of hyaline eosinophilic lumen lining

toma and ameloblastic odontoma (Fig. 5). The lumina of the tubule-like structures that give the adenoameloblastoma its name are empty when true cross sections are viewed. Not infrequently, however, a pinkish-staining material, presumably a secretion of the tall columnar duct cells, can be seen lining the lumina. Several authors have considered this material to be a pre-enamel. Both Miles and Lucas have pointed out the greater similarity of the mural cell to the ameloblast than to the cell of the ameloblastoma. For this reason, Lucas believes that the adenoameloblastoma arises (if we are interpreting him correctly) from the "pre-ameloblast," that is, the ameloblast prior to the organizing stage,[8] and, consequently, he has called it a tumor of enamel organic epithelium. Most of these tumors are associated with the formation of minute amounts of calcified material, but its genesis is probably dystrophic, similar to that seen in craniopharyngioma (hypophyseal ameloblastoma). In many respects, the adenoameloblastoma has a clinical behavior and history similar to that of ameloblastic odontoma and ameloblastic fibroma, especially with regard to age and nonrecurrence.

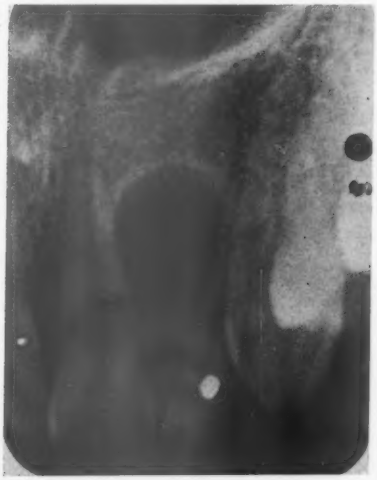

Fig. 1.—Case 1. Radiograph of lesion between maxillary central and lateral incisors. Close examination will reveal some evidence of calcification (see arrow). Both of these teeth were vital.

To determine the nature of the pinkish hyaline material, special stains were employed. The Alcian blue and Schiff stains revealed that the material secreted by the mural cells is acid mucopolysaccharide. This seems to corroborate the view that this material is "pre-enamel," in view of the work of Wislocki and his co-workers[9, 10] indicating that acid mucopolysaccharide is elaborated by ameloblasts and enters the enamel at the time of calcification.

CASE 1

An 18-year-old white girl presented in December, 1953, with an asymptomatic swelling in the upper left anterior region. Radiographs revealed a radioulcency between her upper

left central and lateral incisors. Both teeth were vital, although the lateral incisor had a small lingual pit amalgam filling.

Anesthesia was established by local infiltration. A mucoperiosteal flap was elevated on the labial aspect of the maxillary left central and lateral incisors.

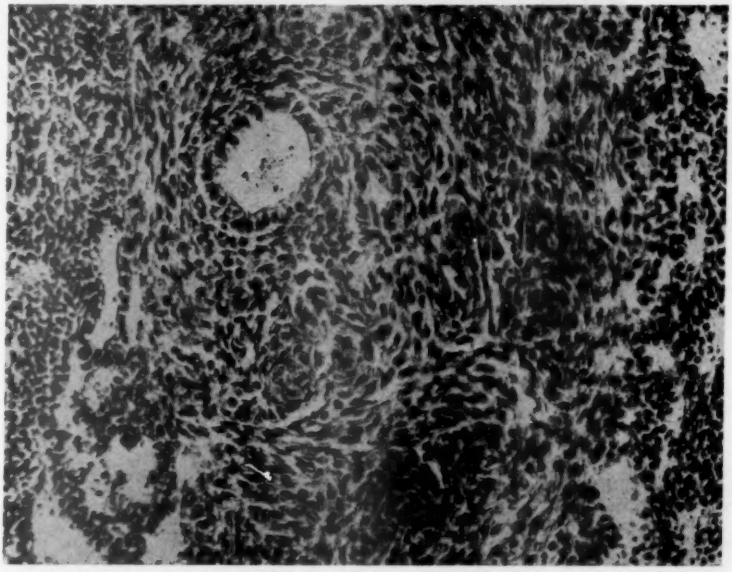

Fig. 2.—Photomicrograph of lesion removed in Case 1 reveals characteristic ductlike structures.

After removal of a portion of the labial bony plate, the lesion was readily visualized and enucleated intact. The mucoperiosteal flap was sutured back into position. (See Figs. 1 and 2.)

Frequent postoperative checkups revealed an uneventful course of healing, with complete bony regeneration within six months. There has been no recurrence to date.

CASE 2

A 13-year-old, well-developed, well-nourished white girl was referred to the oral surgery clinic because of severe pain in the area of her unerupted upper left cuspid. The pain was first noted during the month of November, 1956, and had persisted for approximately three months.

Oral examination revealed a swelling of the labial mucous membrane above the upper left deciduous cuspid. Extraorally, the swelling was also in evidence below the left eye in the area of the canine fossa. The tip of the impacted cuspid was thought palpable just above the apex of the deciduous cuspid. (See Figs. 3 to 5.)

Radiographs revealed a radiolucent area around the crown of the unerupted left cuspid. Electric pulp tests showed the teeth in the area to be vital.

The patient was premedicated with Nembutal sodium, and the surgery was performed under local infiltration and block anesthesia. A large mucoperiosteal flap was raised with some difficulty, for the tumor had perforated through the thin buccal cortical bone and was adherent to the flap. The tumor was peeled from its bony crypt and placed in 10 per cent formalin. The unerupted cuspid was extracted intact, and the incision was closed with 000 silk interrupted sutures.

Fig. 3.—Case 2. Radiograph of cystlike radiolucency about crown of impacted cuspid tooth. This cystic tumor did not contain fluid.

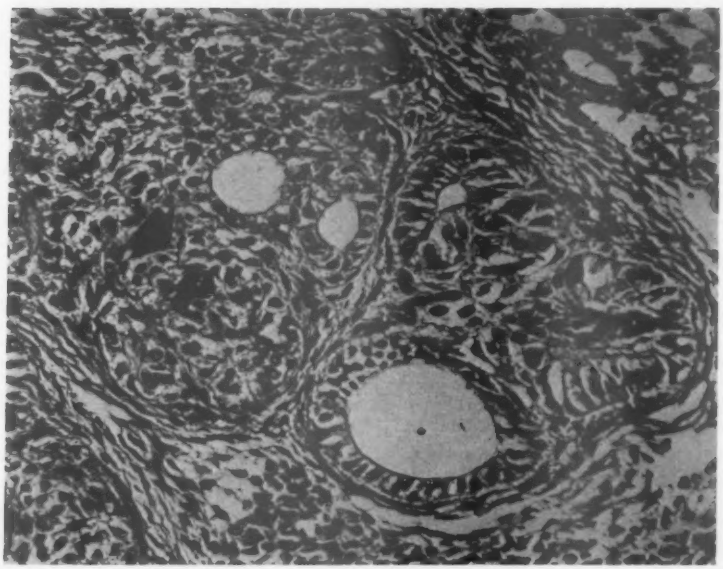

Fig. 4.—Photomicrograph of lesion removed in Case 2 demonstrates numerous ductlike structures, most having been cut in true cross section. At arrow, note small focus of calcification.

The patient was seen four days postoperatively, at which time the sutures were removed and the area was examined. The patient was asymptomatic, except for a slight area of ecchymosis on the labial mucosa opposite the cuspid.

Grossly, the tumor was a partially encapsulated mass, 3 by 2 by 2 cm. in size. The cut surface showed a large cavity filled with irregular projections. There was no fluid within the cavity.

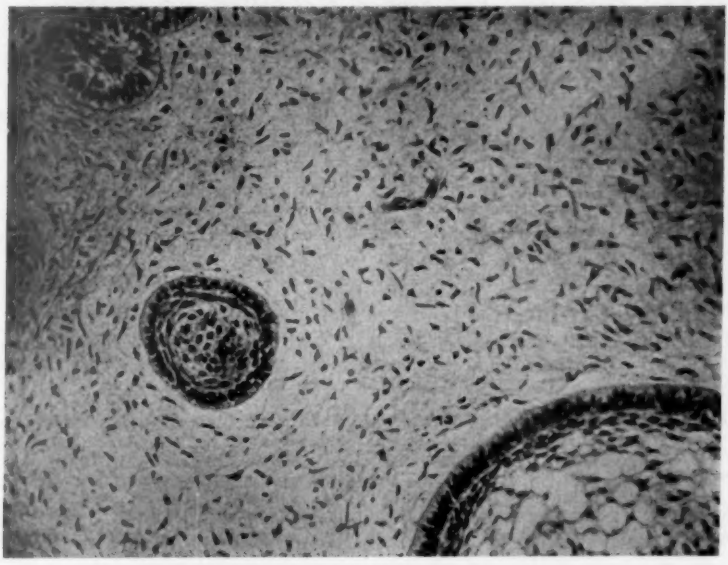

Fig. 5.—Note similarity and differences between the ameloblastic odontoma from a cow's jaw and the adenoameloblastoma. Note the similarity in cell appearance. However, the presence of a stellate reticulum and the reversal of nuclear polarity clearly differentiate these lesions.

Both biopsy specimens were quite similar microscopically. They differed only in degree. In Case 2, the lesion, which was associated with an unerupted tooth, was cystic but without fluid. Case 1 consisted of a solid mass. The most remarkable feature was the presence of large numbers of tubular structures occurring at random throughout the tumor. These ductlike structures, when they were viewed in true cross section, were lined by tall columnar cells. Their nuclei were polarized toward the base of the cell. Several of the lumina contained a pink hyaline-like material that appeared to be formed by the columnar cells. Mucin tests were negative, but Alcian blue revealed the presence of acid mucopolysaccharide. Occasional foci of calcification could be seen.

DISCUSSION AND SUMMARY

Sixteen cases of a lesion described as adenoameloblastoma have been published. We have added two new cases.

Analysis of the cases published indicates that the lesion is twice as common in females and that it occurs about as commonly in either jaw, but more frequently in the incisor-cuspid-premolar areas. It is nearly always found in the second decade of life. Conservative surgery apparently ensures a cure.

The pink homogeneous material elaborated by the ductlike cells, having been identified as acid mucopolysaccharide, suggests that the tumor arises from enamel organ epithelium. This would tend to support the argument of Lucas. Normally there is a shift in centriole and Golgi apparatus as well as a change in alkaline phosphatase activity in normal ameloblast maturation, neither of which can be well demonstrated on already blocked material. If an appropriately fixed specimen of one of these lesions were examined for these changes, perhaps more light could be shed on its ultimate source.

The authors wish to thank Dr. H. B. Clark, B. Gilbertson, and R. Burke for their information in the clinical aspect of these cases and Mrs. H. Schauer and Mr. J. Rothenberger for their technical assistance. Additional thanks are expressed to Dean William Crawford for his encouragement in this study.

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MUCUS-SECRETING TUMOR IN THE CHEEK

Report of a Case

John Hertz, M.D., Stockholm, Sweden

MUCUS-SECRETING tumors are extremely rare. The first published case seems to be the one recorded by Volkmann in 1895. In 1948 Linell[6] was able to collect sixty-nine reports from the entire literature, to which he added twelve cases of his own; his name for the growth was "mucus-secreting and cystic epidermoid carcinoma of the mucous and salivary glands."

Linell's presentation includes two cases of his own in which the tumor was located in the jaw and showed destruction of the bone. In addition, four cases of this very rare location have been reported in the literature by Lepp,[5] Bossart,[1] and Rawson, Howard, Royster, and Horn.[7] In 1952 I added four of my own cases.[3] These ten cases seem to be the only ones on record in which a mucus-secreting epidermoid tumor was located in the jaw.

Location in the oral mucosa seems also to be extremely rare. In the previous literature only three cases are reported in this location,[2, 4, 8] and in all of these the tongue was involved. There is one case on record in which the tumor has been located in the lower lip.[8]

CLINICAL DATA (TABLE I)

All the cases recorded in the literature, as well as the present case, concern females. Skorpil's case in which the tumor was located in the lower lip concerned a male. The patients reported in the literature have been 16, 68, and 85 years old, respectively, when the condition was noticed, and in the present case the patient was 48 years old. The patient with the tumor in the lower lip was 43 years old. In the only cases reported in the literature in which it has been possible to obtain any statement concerning the duration of the lesion, it had been six months and twelve years, respectively; in the present case the duration of the condition has probably been eighteen months.

PATHOLOGY

The mucus-secreting tumors are built up of a stroma consisting of a partly hyaline connective tissue of varying abundance which supports irregularly outlined, mostly solid and cystic epithelial islands and strands of

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TABLE 1

AUTHOR	SEX	AGE	DURATION	LOCATION OF THE LESION	SYMPTOMS	TREATMENT	SUBSEQUENT COURSE	OUTCOME
Kamprath[4]	F	68	6 months	Right side of base of tongue	Tumor	Extirpation	Recurrence 10 months later; re-operation	Not stated
Curtis and Razemon[2]	F	16	Approximately 1 year	In midline of inferior side of tongue	Firm painless tumor	Extirpation	Recurrence 5 months later; re-operation	No recurrence during follow-up period of 5 years
Skorpil[8]	F	85		Left side of tongue	Firm tumor			Accidental finding at autopsy
Skorpil[8]	M	43	12 years	Buccal side of lower lip	Tumor, the size of a prune	Extirpation		No recurrence during follow-up period of five years
Hertz[3]	F	48	Probably 18 months	Mucosa of cheek	Painless tumor	Extirpation plus irradiation		Operated upon recently

epithelial cells, some of which contain mucus. The epithelial cells are abundant; they are polygonal and medium-sized, poor in chromatin, and occasionally vacuolated with a varying degree of squamous-cell differentiation, but very frequently a high degree of differentiation is in evidence. Occasionally the cells in solid columns show a slight tendency to a whorllike arrangement with an increasing degree of keratinization toward the center of the islands. In several places the peripheral parts of the epithelial areas are lined by a layer of cylindrical cells forming palisades. The nuclei are well defined, ovoid,

Fig. 1.—Photomicrograph of mucus-secreting tumor. (Magnification, ×42.)

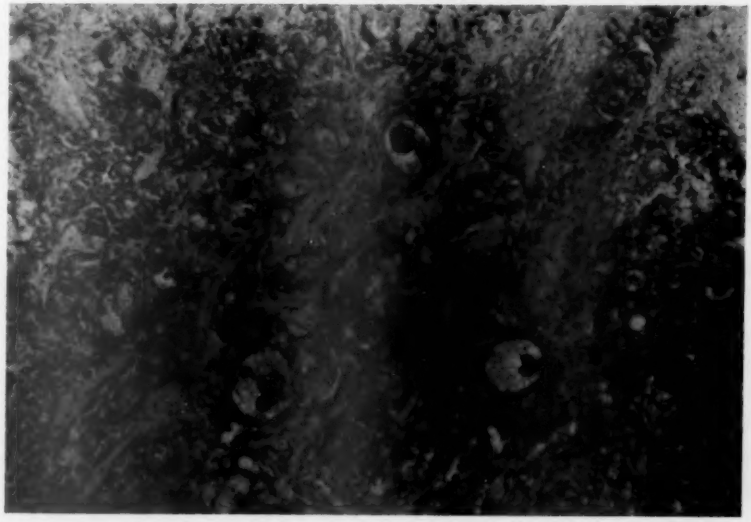

Fig. 2.—Photomicrograph of mucus-secreting tumor. (Magnification, ×84.)

and medium-sized with distinct nucleoli, and in the peripheral parts of the epithelial areas they are located in the basal parts of the cells. The cytoplasm is abundant and pale staining, making the cells assume a hypernephroid character. There is a more or less pronounced cellular polymorphism; the number of mitotic figures is usually small.

The secretion of mucus is a constant and typical feature. When stained with mucicarmine (Figs. 1 and 2) or toluidine blue, the mucus appears as small droplets located in the part of the cells most distant from the stroma. Mucus-filled cysts surrounded by goblet cells are occasionally seen; these cysts may reach a considerable size. In some places the mucus gives the cells a star-shaped appearance, and a stellate reticulum may be formed in the central parts of the epithelial areas. For this reason, and because of the arrangement of cylindrical cells in palisades in the peripheral part of some of the epithelial areas, the histologic over-all pattern may be highly suggestive of an adamantinoma.

The histologic pattern of the mucus-secreting tumors often reveals an invasive growth, despite a comparatively high degree of differentiation.

DIAGNOSIS

The diagnosis is difficult and requires a biopsy.

CASE REPORT

The patient was a 48-year-old woman who sought medical advice for a node in the mucosa of the left cheek in the neighborhood of the papilla of the parotid duct.

For eighteen months she had felt as if the buccal mucosa was pressed between the molar teeth during mastication, for which reason her dentist decided to remove a tooth. When administering the anesthetic, the dentist discovered the node, which was painless.

Examination.—Examination revealed a firm lobulated node, slightly larger than a hazelnut, in the left cheek, corresponding to the region of the lower third molar. The node, which was not tender, was adherent to the mucosa and at the top of it two small irregular ulcers were present. There was no infiltration of the parotid gland.

Routine examination was essentially negative. The regional lymph nodes were not enlarged. Examination of the pharynx, epipharynx, larynx, and nose was negative, as was the x-ray examination of the chest.

Hemoglobin was 75 per cent, and the sedimentation rate was 40 mm. per hour.

Treatment.—The tumor was excised, and irradiation was given postoperatively.

Pathology.—The excised tumor, the size of a hazelnut, seemed to be well demarcated; it was grayish white and slightly lobulated.

Histologically, the tumor was a mucus-secreting epidermoid carcinoma belonging to the group of mucus-secreting and salivary gland tumors, and staining for mucicarmine was positive. On one side the tumor was lined with a squamous epithelium which presented no pathologic features.

Diagnosis.—Mucus-secreting tumor with histologic evidence of malignancy.

COMMENTS

In this case a painless slow-growing tumor in the buccal mucosa was diagnosed histologically as a mucus-secreting epidermoid tumor. Histologically, the typical features of this very rare kind of growth are the presence of epidermoid cells and the secretion of mucus.

SUMMARY

After a brief outline of some historical data concerning the very rare mucus-secreting epidermoid tumor, a case is reported in which this kind of growth has taken its origin from the buccal mucosa. The typical histologic features, consisting of the coincidence of epidermoid cells and mucus secretion, are summarized.

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SINGLE-POINT INTERMITTENT ACTION FOR CUTTING SERIAL SECTIONS OF CALCIFIED BONE AND TEETH

James M. Klinkhamer, D.M.D., and Benjamin Spector, M.D., F.R.M.S.(Eng.), Boston, Mass.

A PRACTICAL method of preparing ground sections of teeth and bone based on a single-point intermittent chiseling action is described. Planing and polishing are not necessary for routine ground sections, but under conditions in which sections are not allowed to come in contact with water additional planing and polishing can be achieved with the apparatus described in this article.

The apparatus is built around a Minot rotary microtome. A shaft assembly carrying a circular saw blade is mounted on the base of the microtome (Fig. 1). The shaft replaces the position previously occupied by the microtome knife. The circular saw blade, therefore, runs perpendicular to the object carrier. The microtome itself and the added shaft assembly are motor driven. The microtome rotates at low r.p.m. (60) and the saw blade at high r.p.m. (6,000). The cycling microtome will move the object carrier up and down and simultaneously in a forward direction. In this way, the object will be fed automatically into the revolving saw blade.

A second attachment to the microtome is a rack-and-pinion arrangement to allow the object carrier to be moved in a lateral direction. After the first cut has been made, the width of the saw cut is measured with the aid of a microscope fitted with a reticle in the eyepiece. Next the object carrier is moved laterally over a distance equal to the width of the saw cut plus the desired thickness of the ground section. Before successive cuts can be made, copper shims are inserted in the saw cut and fixed in place with melted paraffin to provide support for the prevention of cracking during the subsequent cuts.

A rotary microtome adapted as described performs a micro-dado action of a repetitive nature which is continued until the desired depth has been reached. The depth of every single dado stroke can be set for 1 micron per cycle. The up-and-down movement of the specimen into the revolving saw blade causes the tips of the teeth of the saw blade to work tangentially into a straight line of cutting. The result is a gentle cutting action of only one tooth at a time covering a small distance along the line of cutting. If the height of a tooth of a saw is 100 microns, and the microtome is set for 1 micron feed per cycle, then $\frac{1}{100}$ of

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the total height of the saw tooth tip is engaged in the chiseling action. This is only the extreme tip. No area along the line of cutting is chiseled more than once during a single half-cycle. The action is therefore intermittent and single tipped. This gentle action allows sections to be cut without water cooling, if so desired, and a continuous stream of air provides sufficient cooling.

The use of water and the choice of embedding material are often not applicable to the specimen. Under such circumstances, the thinnest sections can be obtained by using methyl methacrylate for embedding and protection of extremely brittle parts, while a continuous stream of water provides for cooling and the removal of debris. The circular saw blade used here is made of steel; it has a diameter of 5 cm. and a thickness of 300 microns. It is possible to cut large molar teeth in toto. No polishing or further planing is necessary for routine use. The average thickness of the sections is 50 microns with the object-carrier feed set for 1 micron. If the feed speed is set for 10 microns the cutting is done ten times faster, but it becomes necessary to polish the individual sections.

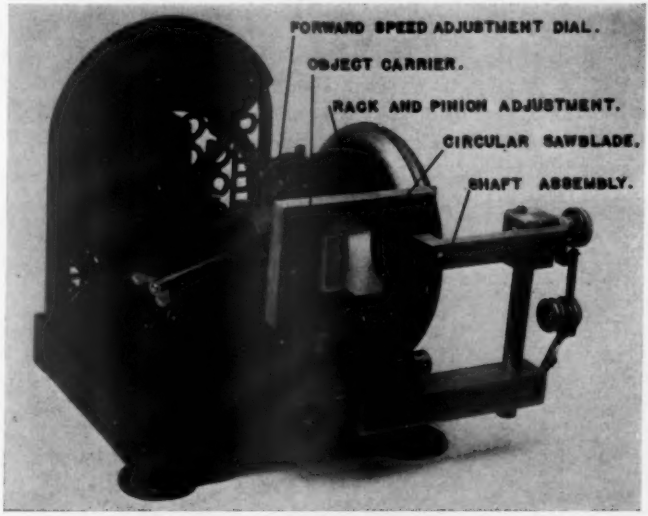

Fig. 1.—Position of shaft assembly for cutting.

Histochemical evaluations of calcified tissues often do not allow the use of water during any stage of the preparation of the sections, and the use of polymerizing materials as an embedding material is prohibited. Under those conditions, the chiseling action of this converted microtome is so gentle that the specimen can be embedded in paraffin and the stream of water as a coolant can be replaced with a stream of compressed air. The intermittent action over the straight line of chiseling keeps the section and the paraffin cool. Removal of debris is the main purpose of the air stream. Compared to methyl methacrylate, paraffin does not give the same protection to the brittle enamel edges

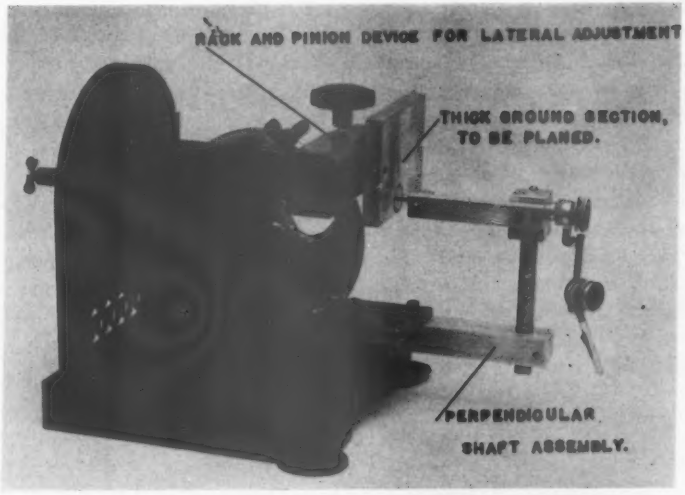

Fig. 2.—Position of shaft assembly for planing and polishing.

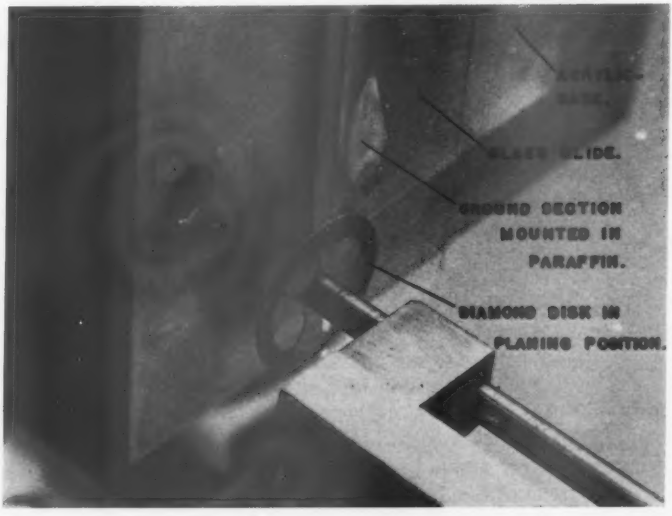

Fig. 3.—Position of specimen, mounted on glass slide.

of teeth. The sections should not be cut any thinner than 150 microns. Therefore, planing and polishing become necessary and are done by rotation of the shaft assembly in such a fashion that the flat surface of the saw blade is parallel with the surface of the object carrier and the specimen (Fig. 2). The steel saw blade is replaced by a diamond disk. The flat abrasive surface of the diamond disk facing the specimen rotates at constant high speed (6,000 r.p.m.), while the specimen passes by moving in an up-and-down direction. The specimen can be conveniently mounted on a flat surface, such as a glass slide (Fig. 3). The diameter of the abrasive disk is kept as small as convenient to secure an intermittent action. The forward speed of the object carrier is set for 1 micron per cycle. The speed of the microtome is 60 r.p.m. Clogging of the abrasive surface of the diamond disk with paraffin is prevented by taking care to mount the specimen to the glass slide with a thin layer of paraffin not any thicker than the final desired thickness of the specimen.

SUMMARY

The following features greatly extend the usefulness of this method: a circular saw blade which cuts along a straight line; an intermittent cutting action which keeps the temperature down to a minimum; a single-point chiseling action which minimizes the friction and which is effective with paraffin used as an embedding medium; the efficient use of copper shims for necessary lateral support. The attachment of workable units to a readily available Minot microtome, as already described, affords a method for the preparation of single or serial sections of teeth and bones for careful study interpretation.

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ENDODONTICS

BONE REPAIR FOLLOWING ENDODONTIC TREATMENT IN AN EXCESSIVELY TRAUMATIZED MOUTH

Report of a Case

G. C. Hare, D.D.S., Toronto, Ontario*

ON AUG. 6, 1955, an 11-year-old girl was involved in a motor accident in which her teeth were driven against the dashboard of the car. The following is a description of the condition of the patient's mouth immediately after the accident as reported by D. J. DeLuke, D.D.S., of Schenectady, New York: "The mandibular incisors were displaced lingually at 90 degrees. The lingual alveolar plate of bone was displaced. All teeth except the right lateral incisor were attached to the displaced bone (Fig. 1). I returned the bone and teeth to normal position and wired the four anterior teeth to a stabilizing bar."

The girl returned to Toronto, Ontario, after being released from the hospital, but she did not present at the office until March 6, 1956. At this examina-

Fig. 1.

*Immediate past-president of the American Association of Endodontists.

tion the teeth were abnormally mobile, a draining sinus was evident distal to the mandibular left lateral incisor, and evidence of a previous sinus was noted on the labial side distal to the right lateral incisor. Thermal and electric tests failed to produce a reaction from the pulps of the four incisors. The radiograph showed regions of rarefying osteitis at the apices of the lateral incisors (Fig. 2). Some evidence of external resorption was seen on the mesial aspect of the right lateral incisor root and also on the mesial aspect of the left central incisor root. Endodontic treatment was started on April 6, 1956. Instrumentation was difficult, due to excessive mobility of the teeth.

Fig. 2. Fig. 3.

Fig. 4. Fig. 5.

In due course the sinus on the left closed, and that on the right remained closed. Successive negative cultures were secured from each root canal. The root canals were obturated by silver points and gutta-percha in a matrix of

sealer cement. The right central incisor root canal was accidentally overfilled 1 mm. (Fig. 3). When the patient was recalled for examination on Oct. 1, 1956, it was noted that the teeth displayed normal mobility and the sinus opposite each lateral incisor had disappeared; a radiograph showed good periapical bone repair. The root resorption did not appear to have progressed during the six-month period (Fig. 4). The patient was recalled for examination fourteen months later. At that time the radiograph showed excellent periapical bone repair, no further extension of the resorption of the right lateral root, but continuing resorption of the root of the left central incisor (Fig. 5). The teeth were symptomless and normally mobile, and the mucosal tissues were of the color and firmness usually associated with a healthy mouth (Fig. 6).

Fig. 6.

This case history is presented for the purpose of emphasizing the repair potential of the tissues of the young mouth. With endodontic procedures in cases of excessive traumatic injury to teeth and surrounding structures, therefore, it is possible to produce a result superior to that obtained with an artificial restoration.

2461 Bloor St. W.

A DILEMMA IN THE DIAGNOSIS OF PERIAPICAL DISEASE

Report of a Case

Jacob A. Englander, D.D.S., F.A.C.D., New York, N. Y.*

THE patient was Mrs. R. C., a woman of about 50 years, whose general health was good.

LOCAL FINDINGS

The mouth required periodontal therapy, to be followed by complete dental reconstruction. Radiographic examination revealed areas of pathosis around the apices of the lower right central and lateral incisors. When tested by the electric pulp tester, the teeth showed no response, indicating that they were nonvital. Clinically, the teeth were rather mobile. It was decided to institute endodontic therapy.

TREATMENT

Root canal therapy was begun on both central and lateral incisors on Oct. 20, 1950 (Fig. 1). Seven visits were required, and treatment was completed on Nov. 6, 1950 (Fig. 2). There were no complications during the course of treatment. Antibiotics were not used, either as a dressing or systemically.

Fig. 1. Fig. 2.

Fig. 1.—Oct. 20, 1950.
Fig. 2.—Nov. 6, 1950.

No apical surgery of any kind was performed. The teeth were placed under observation to check the success of the therapy. (A Vitallium splint, labial and buccal, was placed around these teeth upon completion of the root canal therapy.)

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FOLLOW-UP AND DISCUSSION

On April 25, 1952, a radiograph (Fig. 3) disclosed complete healing of the area seen in Fig. 1. The teeth were firmer and the patient was very comfortable. On Jan. 19, 1953, however, radiographic examination again revealed an area of pathosis about the apex of the central incisor (Fig. 4). (Before proceeding with the discussion, may I point out the change in the type of splint.)

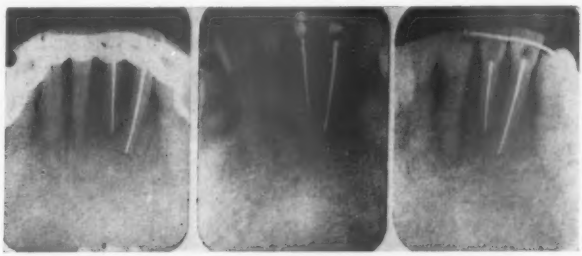

Fig. 3. Fig. 4. Fig. 5.

Fig. 3.—April 25, 1952.
Fig. 4.—Jan. 19, 1953.
Fig. 5.—May 27, 1957.

The problem presented, then, was whether to re-treat the central incisor, perform some kind of surgery to remove the suspicious area, or extract the tooth. Upon reflection, I felt quite confident in the root canal therapy performed. This was the first time that I had ever seen healing of an area following root canal therapy and then a breakdown apically. Upon further clinical examination, it was observed that the central incisor was being traumatized incisally. Since rarefied areas about the apex of a tooth appear due to trauma, it was decided to relieve the premature contact and again place the tooth under observation. The justification for this procedure is evident in Fig. 5, in which it may be seen that the area of pathosis has disappeared (May 27, 1957).

CONCLUSION

Differential diagnosis of apical areas of pathosis is extremely important. Exploration of every means at our disposal will prevent the needless extraction of many teeth. Moreover, past history of treatment is an invaluable aid in diagnosing such a situation as presented here.

5 East 57th St.

RESEARCH

EFFECT OF CARCINOGENIC HYDROCARBONS ON TOOTH GERM HOMOTRANSPLANTS IN FEMALE GUINEA PIG CASTRATES

Harold S. Fleming, D.M.D., Washington, D. C.*

INTRODUCTION

It was reported in a previous communication that growth and development of tooth germs were considerably enhanced when the tooth germs were transplanted to female guinea pig castrates.[8] Epithelial and mesenchymal tissues associated with the anlagen of transplanted teeth continued their biologic activity for longer periods than in intact hosts. This resulted in a retardation of expected aging of cellular structures, and more enamel and dentine were formed. Administration of diethylstilbestrol descreased this superior growth, but in such cases growth and development were superior to the growth and development of transplants in intact untreated hosts.

Expected growth and development of tooth germ transplants were also altered when crystals of carcinogenic hydrocarbons were placed on them before transplantation.[5, 6, 9] Epithelial tissues of the anlagen of teeth, particularly outer enamel epithelium, were extremely labile to the carcinogens. Abundant keratin formations were always produced. In addition, over long periods, particular cells presumably of outer enamel epithelial origin and others arising from certain inner enamel epithelial cells seemed to meet some, if not all, of the histologic and biologic requisites for malignancy in approximately one-fourth of the recovered explants.

Because of the above-mentioned experimental findings, it was of interest to determine events taking place when carcinogenic-treated tooth germs were transferred to female guinea pig castrates. This article constitutes a report an such a study.

METHODS

Techniques of transplantation, including treatment of tissues with carcinogens, have been described.[4-9]

Supported by a grant from the United States Public Health Service, National Institutes of Health, Bethesda, Maryland.

*Formerly Research Associate, Department of Pathology, Yale University School of Medicine; now at Howard University College of Dentistry, Washington, D. C.

Anlagen of guinea pig cheek teeth were considered satisfactory for transplantation prior to calcification and were usually obtained from embryos 25 to 40 days of age. Incisor tooth germs were not used for these experiments.

Transplants were made to the eyes and brains of female guinea pigs about five days after castration and were recovered at particular times from eighteen to about 200 days. They were then fixed, decalcified when necessary, sectioned, and stained for histologic study.

The carcinogens used were 20-methylcholanthrene and 1, 2, 5, 6-dibenzanthracene. A total of 439 female castrates received methylcholanthrene- and dibenzanthracene-treated tooth germ transplants. Of this total number, 219 transplants were made to brains and 210 were made to the eyes. One hundred seventy-two eye transplants and 174 brain transplants were made with methylcholanthrene, and forty-eight eye transplants and forty-five brain transplants were made with dibenzanthracene. With each series, an equal number of castrates received untreated tissues to the respective transplantation sites. Dibenzanthracene was never used alone, and when both carcinogens were used in the same series equal numbers of castrates received tissues treated with each carcinogen as well as untreated transfers.

Each series consisted of tooth germs from the embryos or embryo of a single pregnant guinea pig. Usually two embryos, or possibly one, were obtained from older females, and up to six were obtained from younger animals.

Diethylstilbestrol injections were given as before[9] and consisted of 1 mg. intramuscularly three times weekly, up to and including five weeks. A total of eighty-four animals bearing methylcholanthrene- and dibenzanthracene-treated tooth germs (incorporated in the above total) received diethylstilbestrol injections—forty-three to brains and forty-one to eyes.

RESULTS

Less growth and development were obtained with carcinogenic-treated transplants than with untreated transplants in female guinea pig castrates. Donor tissues from younger guinea pig embryos (about 25 days) usually became totally disorganized within twenty days in castrated hosts. Tissues obtained from older embryos developed more, but there was generally a disorganization of mineralized structures with coronal areas losing much of their morphology. Enamel was poorly formed, and dentine was usually produced in a disorderly fashion with numerous blood vessels and vascular spaces being incorporated in the matrix. Ultimately pulpal areas became filled with a mixture of vascular and osteoid tissue. At times this latter tissue appeared more like cartilage. Figs. 3, 7, and 10 show these pulpal changes under the several conditions of these studies.

Reactions of castrated hosts to treated tissues differed considerably from reactions of normal animals to similarly treated tissues and also from the behavior of castrates to untreated explants. Carcinogenic-treated tissues invoked more striking reactions in castrates than had been observed previously in normal

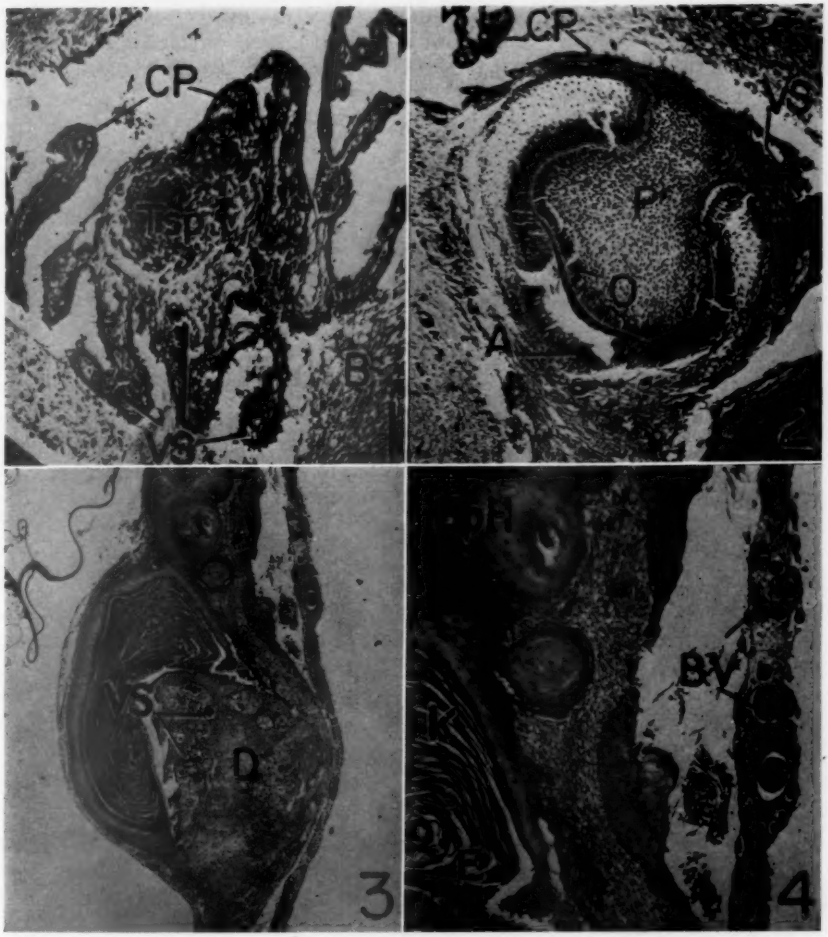

Fig. 1.—Thirty-five-day guinea pig tooth germ treated with methylcholanthrene, transplanted to brain of female castrate, and recovered after twenty-one days. (Original magnification, ×180; reduced ⅓.)

Fig. 2.—Deeper section of tooth germ shown in Fig. 1. (Original magnification, ×130; reduced ⅓.)

Fig. 3.—Thirty-day guinea pig tooth germ transplanted to anterior chamber of female castrate and recovered after eighteen days. Tooth germ treated with methylcholanthrene before transplantation and host received six injections of diethylstilbestrol. (Original magnification, ×35; reduced ⅓.)

Fig. 4.—Higher-power view of section shown in Fig. 3. (Original magnification, ×130; reduced ⅓.)

Key to Symbols

A = Ameloblasts
BV = Blood vessels
B = Brain
CP = Choroid plexus
ChS = Cholesterol slits
Cy = Cysts
C = Cornea
D = Dentine
P = Dental pulp
E = Enamel
Es = Eosinophils
EpC = Epithelial cells
EpH = Epithelial hyperplasia
Epy = Ependymal cells
K = Keratin
L = Leukocytes
Ly = Lymphocytes
O = Odontoblasts
Os = Osteoid
Tsp = Transplant
VS = Vascular spaces

hosts. This was indicated by accumulations of great numbers of acute (polymorphonuclear leukocytes) and chronic (lymphocytes) inflammatory cells in and about the transfers. Numbers of phagocytes filled with cellular debris were also evident. Furthermore, considerably more eosinophils were present under conditions of the present study than had been noted in other experimental conditions. Figs. 6, 7, 10, and 12 demonstrate some of the host responses.

Marked inflammatory reactions by host castrates increased incidence of total resorption, which varied between one-third and one-half of each series. A total of ninety-seven eye transfers and eighty-five brain transfers were recovered. Accumulations of extravascular red blood cells and inflammatory cells were usually the only indications that a transplant had been made. Responses were considerably more vigorous than had been observed when similarly treated explants were made to normal animals. No appreciable difference in resorption was observed between the two carcinogens. Brain transfers of carcinogenic-treated tissues in these castrates, however, resorbed more frequently and completely than did eye transfers. Considerable activity of ependymal cells was noted in cases of resorption of treated brain transfers, and in several instances the histologic picture was that of an ependymoma. Fig. 9 depicts such a reaction of ependymal cells.

When diethylstilbestrol had been injected, accumulations of acute inflammatory cells decreased and chronic inflammatory cells were increased. Total resorption of treated tooth germ explants decreased in the presence of this hormonelike substance, for out of eighty-four animals bearing transplants and also receiving injections tissues were recovered in fifty-six instances. As seen in Figs. 3 and 4, a significant hyperplasia of epithelial components of the transfers rapidly took place after five or six injections of diethylstilbestrol. With more injections (thirteen to fifteen), this epithelial reaction was not as pronounced.

Local proliferation of vascular systems increased in response to these treated transfers in castrates. In brains the activity of the choroid plexus was marked, and responses of iridic blood vessels, on the other hand, were not as great. Under diethylstilbestrol administration, however, activity of vascular systems increased at both transplantation sites. Figs. 1, 4, and 5 depict reactions of host vascular systems.

Keratin formation was decreased, was broader, and stained more heavily with eosin than when treated transfers were made to noncastrates. In addition, these formations did not appear as completely formed as in the latter instances and often presented a granular appearance with nuclear fragments being incorporated in the strands. In addition, a noncellular pink material was found to be closely associated with the keratin on a number of occasions. Eosinophilic granulocytes and large phagocytic cells were present in such areas. In about two-thirds of the recovered tissues, keratin formations were significantly decreased or absent. Figs. 3, 10, and 11 show these keratin formations.

Another point of interest was the loss of morphology of tooth structures in carcinogenic-impregnated transfers. Under the present experimental conditions, pulpal reactions were marked. At times, the dentine matrix proliferated to

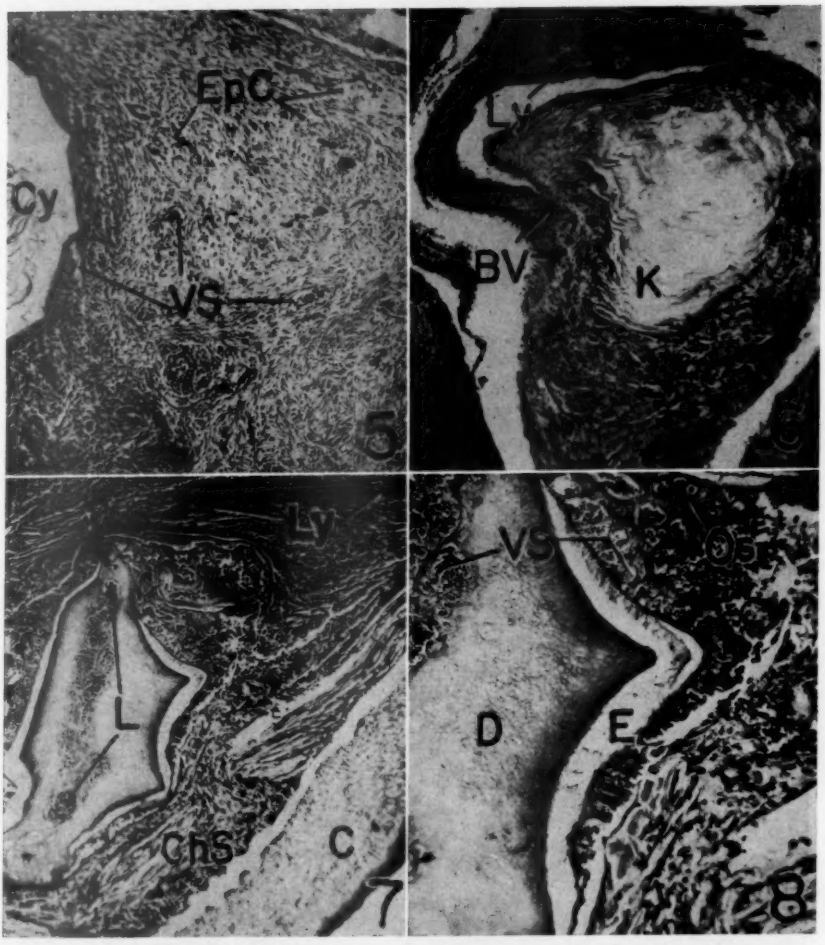

Fig. 5.—Thirty-day guinea pig tooth germ treated with methylcholanthrene and transplanted to brain of female castrate. Fifteen injections of diethylstilbestrol given and transplant recovered after forty-five days.

Fig. 6.—Twenty-eight-day guinea pig tooth germ treated with dibenzanthracene and transplanted to brain of female castrate. Recovered after thirty-five days. (Original magnification, ×110; reduced ⅓.)

Fig. 7.—Thirty-five-day guinea pig tooth germ treated with methylcholanthrene and transplanted to anterior eye chamber of female castrate. Recovered after eighty-six days. (Original magnification, ×110; reduced ⅓.)

Fig. 8.—Higher-power view of section shown in Fig. 7. (Original magnification, ×275; reduced ⅓.)

(For Key to Symbols, see page 785.)

occlude most of the pulp. Often this tissue appeared to be more cartilaginous than osteoid. Vascular spaces were always enclosed in this tissue. In addition, proliferations of angiomatous tissue or vascular spaces occupied areas adjacent to the transplants and also pulpal areas in transfers of about 60 or more days' duration. Figs. 3, 7, and 11 depict this.

Particularly striking were the reactions of ameloblasts which regularly underwent degeneration. Most of these cells lost their cytoplasm, and others

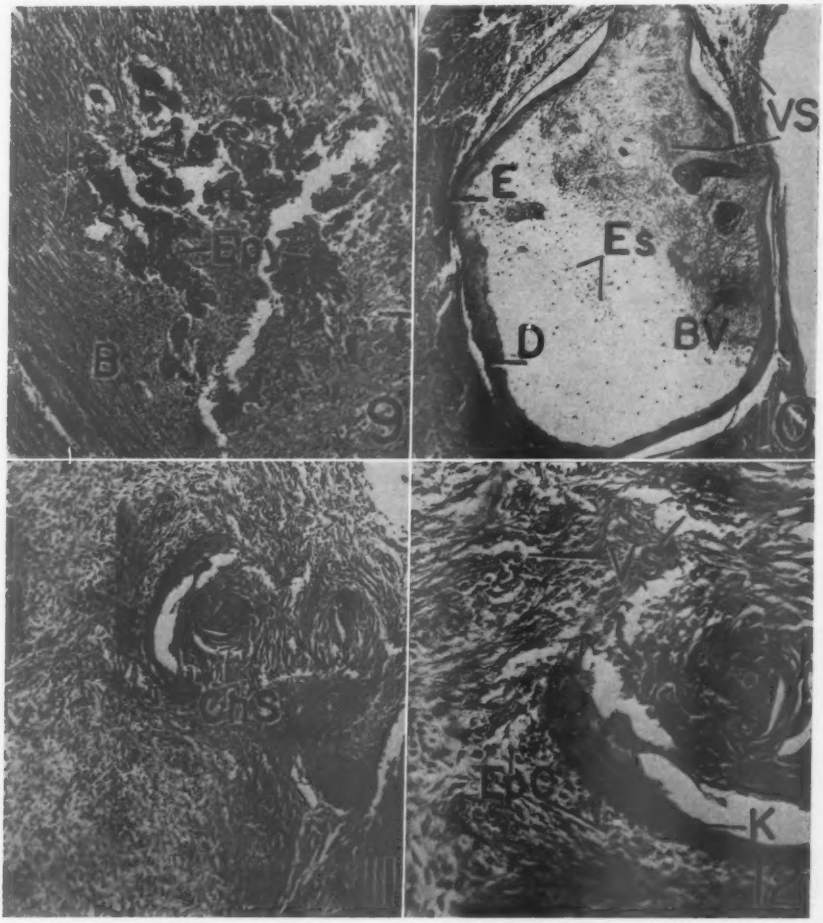

Fig. 9.—Transplantation area in brain of female castrate after sixty-six days.

Fig. 10.—Thirty-five-day dibenzanthracene-treated tooth germ after 104 days in brain of female castrate. (Original magnification, ×130; reduced ⅓.)

Fig. 11.—Thirty-eight-day guinea pig tooth germ after 125 days in brain of female castrate. Tissue treated with methylcholanthrene. (Original magnification, ×130; reduced ⅓.)

Fig. 12.—Higher-power view of section shown in Fig. 11. (Original magnification, ×250; reduced ⅓.)

(For Key to Symbols, see page 785.)

among them became active mitotically and exhibited pleomorphism and hyperchromatism. In some recovered transplants, nothing recognizable was observed except areas of these epithelial cells among which were numerous vascular spaces. Most odontoblasts had disappeared from pulpal areas and were infrequently seen except in transfers recovered after about twenty to thirty days. These cells, when present, were being pushed out of their normal positions by invading vascular tissues.

DISCUSSION

The biologic events taking place in the present experiments had little or no resemblance to those results previously obtained with castrates[8] or in the case of tooth germs transplanted with carcinogenic hydrocarbons.[5, 6, 9]

While it was expected that there might be some alteration in growth and development, the complete alterations were most striking in transfers from younger embryos. These cellular reactions by the hosts to the transplants were initially so vigorous that many transfers were destroyed. Such overwhelming host responses had not been encountered before, except for short periods when contaminated tissues were inadvertently transplanted. These results were even more significant when comparisons were made with parallel untreated transfers in castrates.

Inflammatory responses about tumor masses which decrease with age indicate one of the principal and characteristic defensive measures of hosts.[2] Likewise, a persistence of acute inflammatory cells in and about transfers would explain the increased instances of resorption in these studies. In acute inflammatory conditions, according to Menkin,[12] the presence of leukocytes is due to developing acidosis which, in turn, is referable to a local disturbance in intermediary carbohydrate metabolism. Thus, in the present instance, the hosts' responses may have been the consequences of a continuation of these local metabolic changes at transplantation sites. It is also significant that whenever diethylstilbestrol was administered, such acute inflammatory reactions were diminished.

The constitutional status of castrated hosts hindered acceptance of carcinogenic-treated donor tissues, and, as Greene[10] has indicated, the biologic fate of tissue transplants will vary according to the condition or character of the recipient animals. In fact, the physiologic behavior of hosts was further altered when diethylstilbestrol was administered. This was apparent since the cellular pattern was predominantly one of a chronic inflammatory nature in local responses to these transfers. Thus, it seemed evident that this synthetic substance, although it did not decrease the hosts' cellular responses, altered the type of reaction to the transfers. Horning[11] obtained results of a similar nature in experiments dealing with induction of prostatic tumors by means of carcinogens in castrated mice.

Of extreme significance were the local vascular reactions to the treated transfers. The ability of the choroid plexus to surround tissue transplants at

ectopic locations indicated that changes had taken place along blood brain barriers. Blood vessels in the iris, while reactive in relation to the transplants, were not as proliferative. Such intense vascular responses have not been observed previously.

Most striking were the proliferations of angiomatous tissue directly associated with these transfers. The basic reaction at earlier stages was of a granulomatous nature. Later, especially when diethylstilbestrol had been administered, these vascular changes were histologically similar to hormonal gingival tumors as seen in epulides or in gingivitis gravidarium. Finally, these tissues closely resembled angiomas in their appearance.

It is difficult to explain why there was a decrease in keratin formations arising from these treated transfers, but it is quite possible that this end product of associated epithelial tissues was delayed or inhibited in its formation. Its sporadic development may have been the result of differences in androgenic activity of the adrenal glands following castration. In a study with ovariectomized guinea pigs, these differences in degrees of endogenous estrogen secretions were noted.[1] Also evident in the present experiments was a hyperplasia of epithelial tissues, often fifteen to twenty cells deep as compared with the five- or six-cell layers ordinarily observed. This proliferation is a common observation during early hydrocarbon carcinogenesis,[13] but, as Blumenthal and Hecht[3] state, these cellular changes are not necessarily the precursors of malignancy.

SUMMARY

1. There was less growth of carcinogenic-treated tooth germs than of untreated tooth germs in female guinea pig castrates.

2. There was more resorption with carcinogenic-treated tooth germs in castrates than in noncastrates, and there was less resorption when diethylstilbestrol was injected.

3. Inflammatory responses to treated tissues were greater in castrates than in intact hosts.

4. Cellular responses by the hosts were changed when diethylstilbestrol was injected.

5. Host vascular systems were active about transplants and increased when diethylstilbestrol was used.

6. Angiomatous proliferations were marked in and about the transfers.

7. Keratin formations were significantly decreased or were absent.

8. Epithelial tissues proliferated more in castrates than similar tissues had been seen to do in intact hosts.

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ACETONE-PRESERVED BANK BONE IN RECONSTRUCTION OF THE MANDIBULAR RIDGE*

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ADVANCEMENTS in the field of oral surgery, coupled with improved methods of controlling infection, have created interest in the direction of aid for those persons handicapped by extensive atrophy of the alveolar ridge. With this group of persons in mind, attempts were made experimentally to increase the height and contour of the mandibular ridges of dogs. The bone used in this study was preserved in acetone and formalin. To our knowledge, this represents the first time that bone preserved in this manner has been used in the mouth.

GENERAL BACKGROUND

Attempts to increase the height of the mandibular ridges by the addition of bone to the crest have been reported in only a few instances. Beube and Silvers[1] reported a case in 1936 in which heterogenous (bovine) bone powder was introduced into the mandibular ridge of a 31-year-old woman. This was successful at the end of fifteen months, but no follow-up was reported. Gerry,[2] in 1956, published a case report in which autogenous iliac bone was placed on the crest of the ridge via an intraoral approach. An artificial denture was worn subsequently for eighteen months without any roentgenographic changes being observed within the graft. Costigan[3] used bone paste to fill undercut areas in ridges but did not attempt any procedures involving elevation. Blackstone and Parker,[4] in 1956, reported their experimental work. They employed bone that had been preserved by a "freeze-dried" method and placed this on the crest of the mandibular ridges of dogs. They attained a 30.8 per cent success rate. A similar technic was used on one human being, but at the time of publication no denture had been constructed for use on the newly created

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ridge. This same pair of investigators placed "freeze-dried" cartilage and "freeze-dried" segments of aorta on the mandible. A higher incidence (60.8 per cent) of success was obtained with the use of cartilage. This was attributed to the ease in shaping and adapting the cartilage to the underlying ridge. Bettman[5] introduced cartilage into a pocket created between the ridge of the maxilla and the overlying hypertrophic tissue, thus creating a more substantial denture-bearing area.

PRESENT STUDY

Five mongrel dogs of various weights were selected. To simulate the conditions of resorption found in the mouth of human patients, the appropriate teeth of the dogs were removed and alveolectomy was performed; thus, the entire ridge was removed. Anesthetization was accomplished by the intravenous administration of pentobarbital sodium (Nembutal) in a dose of 25 mg. per kilogram of body weight. In the first animal the airway was established by use of an intratracheal tube, but the oral cavity became congested and it was difficult to work in the mouth; therefore, the tube was removed. As this animal experienced no further difficulty in respiration, the intubation was omitted in the remainder of the dogs.

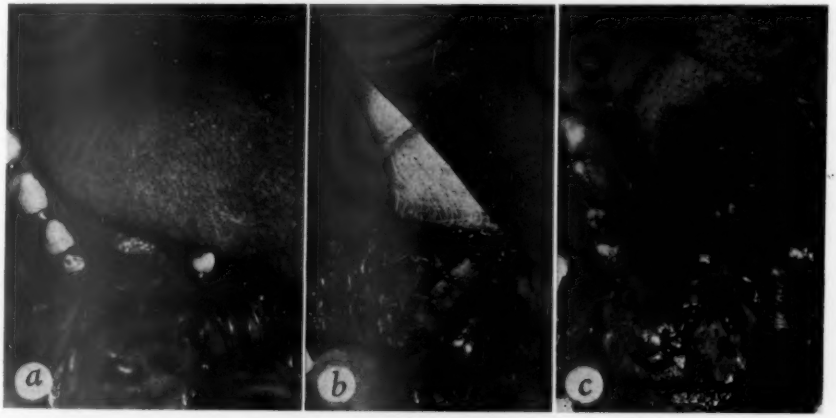

Fig. 1.—*a*, Mandible sixty-two days after extraction of teeth. Note that the alveolar ridge of the mandible was completely removed by alveolectomy. *b*, Method of insertion and retention of the bone grafts. *c*, Appearance immediately after closure of the soft tissue over the bone graft.

The anterior teeth of the maxilla and mandible were removed, as shown in Fig. 1, *a*. The motivating factor for the removal of the maxillary teeth was protective in nature. With these teeth out, interference (on the part of the animal) with the grafts was reduced considerably.

Selection and Preservation of Grafts.—To obtain bone for this work, sections of ribs were removed from other healthy dogs at necropsy. This bone

was removed without undue regard to asepsis, and all soft tissue was discarded. The bone was treated as has been described by Sabanas and co-workers.[6] Immediately after removal, the bone was transferred to a small wide-mouth bottle containing 10 volumes of acetone. The acetone was changed twice in a twenty-four-hour period, after which the bone was placed in a 1 per cent solution of formaldehyde. The study by Sabanas and associates had shown that acetone would not kill spore-forming bacteria, so this was accomplished by immersion in the solution of formaldehyde for six hours. After this, the bone was removed from the formaldehyde solution with sterile thumb forceps and placed into a container of acetone. This bone was then stored at room temperature for periods up to twenty-seven days.

Preparation of Grafts.—At the time of operation, it was necessary to remove the acetone from the bone. This was accomplished by taking advantage of the volatility and solubility of acetone. On the evening preceding the operation, the graft was removed from the acetone with sterile forceps and placed in a dry sterile Petri dish, thereby allowing the chemical to evaporate. On the morning of the operation, the bone was placed in a sterile pan containing an isotonic solution of sodium chloride, thus completing the removal of the excess acetone. Prior to their placement, the grafts were decorticated and, in effect, were split-rib grafts. Theoretically, this allows faster revascularization of the graft, since an open surface is in contact with the bed.

Surgical Application of Grafts.—An average of fifty-nine days elapsed before the dogs were subjected to the second phase, or the actual grafting procedure. The anesthesia was the same as for the extractions. An incision was made over the crest of the mandibular ridge, extending from the first premolar on the right to the first premolar on the left. The tissues were reflected by a flap method, exposing the mandibular bone. The underlying bone was freshened by means of a rongeur. The graft was then inserted (Fig. 1, *b*). The grafts elevated the ridge approximately 0.5 cm. and were held in place by means of tantalum wire (000) placed circumferentially around the mandible. The tissue for closure was obtained by sacrificing a portion of the labial gingival sulcus (Fig. 1, *c*). Healing was rapid and uneventful in all but one of the dogs. In this one instance, the incision opened on the fourteenth postoperative day and the graft was exposed until the animal was killed ninety-five days later. In all instances, 300,000 units of procaine penicillin (Duracillin) was given daily for the first three postoperative days.

The animals were killed at intervals ranging from seventy-five to 170 days. The mandible was removed, and roentgenograms and histologic sections were made. The bone was decalcified in a solution containing concentrated hydrochloric acid, concentrated formic acid, and distilled water. Hematoxylin and eosin were used for staining.

RESULTS

It was found that three of the five dogs still retained portions of the grafts at the time of necropsy. Study of the roentgenograms, however, gave evidence

that the grafts were undergoing resorption in these three dogs. Dog 1 retained a segment for seventy-five days, after which the animal was killed. Dog 3 displayed bone in the process of sloughing and also bone that was well attached (Fig. 2). Only the cortical layer of the graft remained in Dog 4 (Fig. 3).

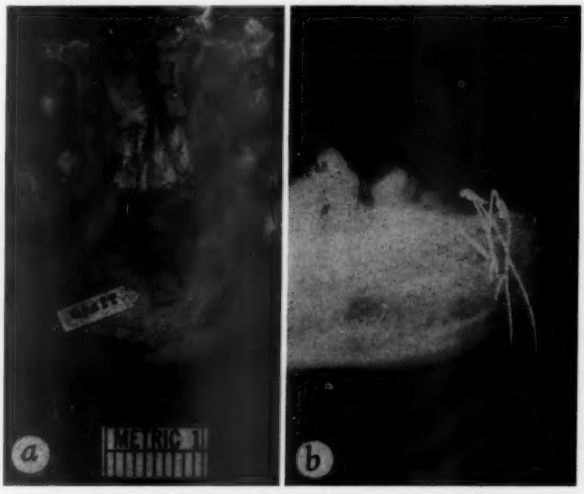

Fig. 2.—*a*, Resected mandible, showing a portion of the graft being sloughed after 125 days. *b* Roentgenogram of the same mandible. The small white arrow demonstrates the piece of bone that was sloughing, and the large black arrow shows grafted bone still intact.

Fig. 3.—Roentgenogram of resected mandible 170 days after operation. Only the cortical layer of the graft remains.

The grafted bone in Dog 2 had sloughed when the animal was killed after ninety-five days. The implant in Dog 5 had been resorbed when this dog was killed; microscopic sections through the region formerly occupied by the graft in this animal revealed dense, collagenous, fibrous tissue (Fig. 4). Table I summarizes the findings in each animal.

TABLE I. DATA IN EXPERIMENTAL APPLICATION OF BONE GRAFTS TO THE MANDIBULAR RIDGE: FIVE DOGS

DOG	DAYS AFTER EXTRACTIONS	AGE OF PRESERVED BONE (DAYS)	LENGTH OF LIFE AFTER GRAFTING (DAYS)	FINDINGS
1	57	27	75	Part of graft intact, part gone
2	62	21	95	Graft sloughed
3	63	2	125	Part of graft sloughing, part intact
4	55	14	170	Cortical portion of graft left
5	58	8	170	Graft gone

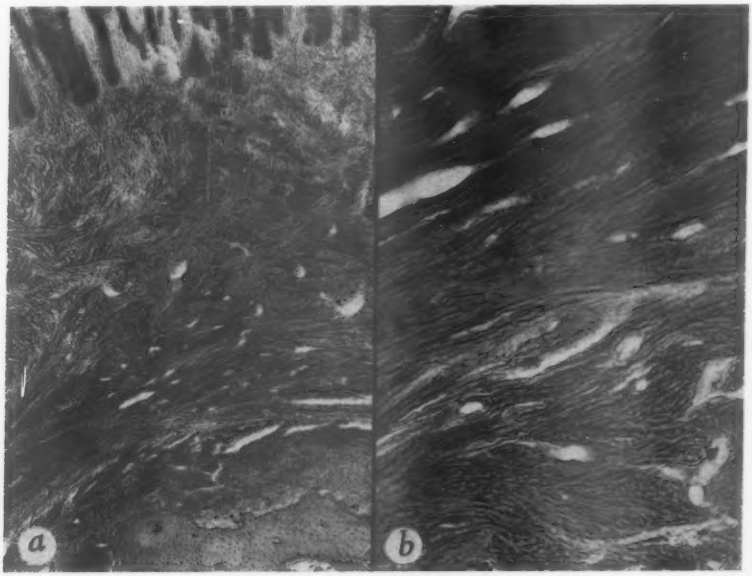

Fig. 4.—*a*, Mandible 170 days after the grafting procedure. The region between the overlying mucous membrane and the underlying bone was formerly occupied by the bone graft. Dense, collagenous, fibrous tissue has now replaced the graft. (Hematoxylin and eosin stain. Magnification, ×30.) *b*, Higher magnification of the central portion of *a*. (Hematoxylin and eosin stain. Magnification, ×100.)

COMMENT

This study was conducted as a forerunner to the possible establishment of a practical method of rebuilding the resorbed mandibular ridge in man. The original plan was to apply this method to persons unable to retain an artificial denture because of atrophy of the mandibular ridge. However, because of the knowledge gained in this experimental study and because of the relatively low percentage of success, this particular method was not considered feasible for human beings.

When animals are used for intraoral studies, the interpretation of results must be guarded. Lack of oral hygiene and lack of cooperation are the

prominent factors. The animals would chew on the bars of the cage door, which constituted a constant source of irritation to the normal healing process.

One of the chief drawbacks in rebuilding the mandibular ridge is the apparent difficulty in shaping and adapting the bone to the ridge. This prompted Blackstone and Parker to abandon the use of bone in favor of cartilage for this work.

Two important concepts have been shown in this study. First, the method of preservation of the bone employed is technically sound; if this bone were used in a region free of infection, in which trauma is not severe, success might be expected. In oral surgery, the packing of postoperative cystic defects with bone chips would represent such a region. Second, these results reaffirm the basic fact that animal research and experimentation always should be a preliminary step before any unproved technique is applied to man.

SUMMARY

An attempt was made to rebuild the ridges of the mandibles in five dogs. The bone that was used was preserved in an efficient, easy, and economic manner. The main problem was to determine, through animal experiments, the feasibility of carrying out a similar procedure in human beings in whom atrophy of the mandible makes it impossible to retain artificial dentures.

The five animals were treated by application of a bone graft to the ridge and then were observed for various intervals. At the time of necropsy, three dogs still had portions of the grafts remaining; roentgenographically, however, these grafts were undergoing resorption.

The results of this study were not successful enough to warrant application of this technique to human patients.

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USE OF TREPHINES IN ORAL SURGERY

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TREPHINES, which have been used for many years in orthopedic surgery and neurosurgery, are crown saws for the removal of circular discs of bone. Because of their usefulness in making a differential diagnosis and in research to study the healing of extraction sockets, these instruments can be a valuable addition to the armamentarium of the oral surgeon.

Although the mandible and the maxilla are not often the sites of malignant tumors, the cancellous portion of these bones is frequently the site of benign enostoses, benign tumors, or variants of the condition known as fibrous dysplasia. It is not always necessary to treat these benign lesions surgically, but a definite diagnosis is generally indicated and is always imperative when malignant conditions are suspected.

Various sizes of trephines are available (Fig. 1) ranging in diameter from a few millimeters to an inch or more. Some of them are adaptable to the dental handpiece while others are made to fit into a Stryker saw. Although the blade of the trephine may be too thick, this can be corrected by grinding down the outside of the blade to make the cutting surface thinner. The thinner the blade, the less traumatic the procedure will be.

A case in which this trephine technique was used for diagostic purposes is shown in Figs. 2 and 3. The radiographic diagnosis was periostitis with reactive bone formation at the angle and inferior border of the ramus of the mandible. An immediate postoperative radiograph (Fig. 3) shows the area from which the bone plug biopsy was obtained. The pathology report of the specimen was consistent with the radiographic diagnosis.

At the University of Texas Dental Branch, our most frequent use of trephines is in research with clinical patients. Bone substitutes, including cultured calf bone chips[1] and anorganic bone chips,[2] as well as autogenous and homologous bone chips, are placed in healing extraction sockets and these sockets are biopsied periodically by the method demonstrated in Fig. 4. Extraction sockets containing only a blood clot constitute controls for these studies.

A small slit incision in made in the mucoperiosteum directly opposite the healing alveolus which is to be biopsied. The mucoperiosteum is freed around the small incision so that the trephine in the dental handpiece can be easily

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inserted without tearing the mucosa. With light pressure applied against the bone and with liberal amounts of saline administered to prevent bone necrosis, the trephine burrows into the bone very easily. When withdrawn, it contains the small bone plug. This can be teased out of the trephine with the sharp end of an explorer inserted into the small hole designed for this purpose in

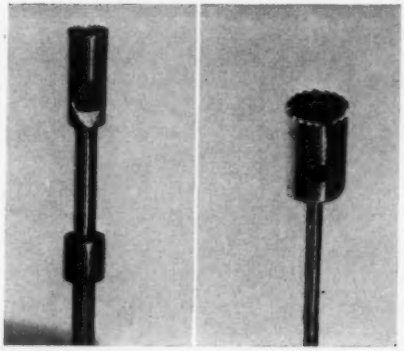

Fig. 1.—Trephines, 4 mm. and 7 mm. in diameter.

Fig. 2.—Preoperative radiograph. Note periostitis with reactive bone formation at angle and inferior border of mandible.

the proximal end of the instrument. A bone plug obtained by this method from a fourteen-day healing upper lateral incisor alveolus is pictured in Fig. 4, *B*. An immediate postoperative radiograph is taken to locate the exact site from which the specimen was obtained.

It is essential to have this information if we are to determine whether or not the area of interest has been biopsied. Because osteogenic activity in the healing extraction socket is faster in some areas than in others, it is also important to determine the depth from which the specimen was obtained. Osteogenesis occurs first in the fundus region and last in the center of the alveolus.

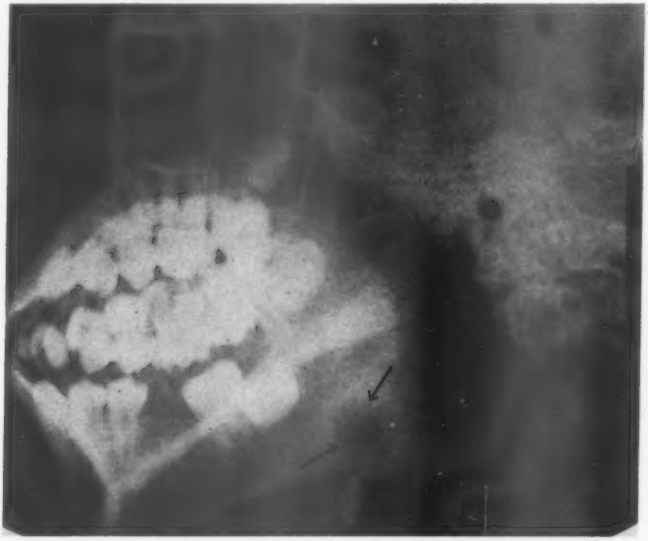

Fig. 3.—Postoperative radiograph. Note trephine defect in angle of mandible.

A study of this type does not necessitate separate surgical procedures to obtain specimens when full-mouth extractions are carried out in one quadrant at a time. In this way, a week or two after the teeth of a quadrant are removed, specimens may be obtained from these healing sockets at the same time that the teeth of the opposite quadrant are extracted. The upper lateral incisor alveoli are the most ideal sockets for study because of their anatomic location, which allows easy access and minimizes the danger of nerve injury and maxillary sinus perforation.

Another method of study that can be used is to select a case requiring multiple extractions and alveolectomy and handle it as a two-stage procedure. In the first stage the teeth are extracted and the sockets are filled with the bone chip implant to be studied. The second stage consists of securing the specimen with a trephine and completing the alveolectomy.

SUMMARY

The oral cavity offers a unique location for studying the healing of bone and the value of the various types of bone chip grafts. The trephine technique

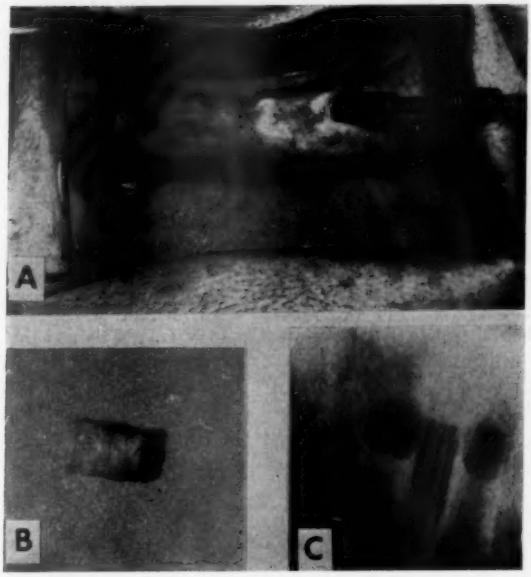

Fig. 4.—*A*, Small dental trephine inserted through incision in mucoperiosteum and into healing upper lateral incisor alveolus.

B, Specimen from upper lateral incisor alveolus.

C, Immediate postoperative radiograph. Note that specimen was taken from lower third of upper incisor alveolus.

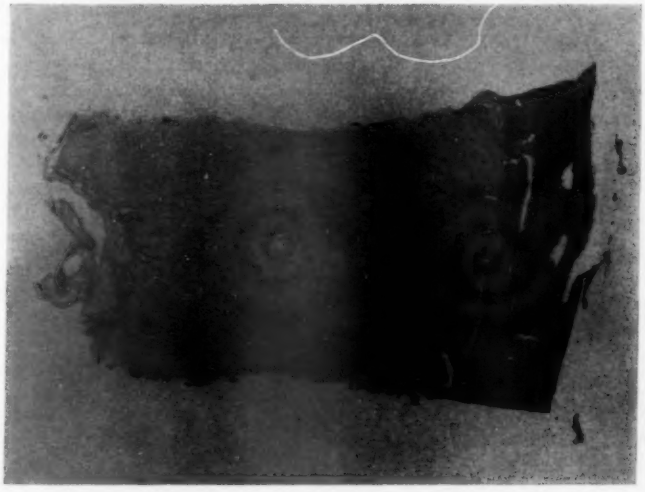

Fig. 5.—Photomicrograph of specimen shown in Fig. 4, *B*. Note the labial cortical plate and the fibrous callus which has replaced the blood clot.

can also be applied to the study of bone substitutes as possible inductors of new bone formation in cystic cavities, in tooth extraction sockets, and on resorbed alveolar ridges. It is hoped that the simple trephine technique described here will be an aid in the diagnosis of suspicious bone lesions, and that it may be an adjunct to the study of the healing of extraction sockets, thereby giving some insight into the etiology of alveolitis.

REFERENCES

1. Tucker, E. J.: Studies on the Use of Cultured Calf Bone in Human Bone Grafts, Clinical Orthopaedics No. 7, Philadelphia, 1956, J. B. Lippincott Company, p. 171.
2. Losee, Fred L., and Hurley, Lloyd A.: Successful Cross-Species Bone Grafting Accomplished by Removal of the Donor Organic Matrix, Research Report Project NM004-006.09.01, Vol. 14, pp. 911-948, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland, 1956.

PROFESSIONAL NEWS ITEMS

The New York Institute of Clinical Oral Pathology, Inc.

The seventh Herman L. Reiss Memorial Lecture will be held at the New York Academy of Medicine Building, 2 East 103rd St., on Monday, Oct. 27, 1958, at 8:30 P.M.

The essayist will be Seymour J. Kreshover, D.D.S., M.D., Ph.D., Associate Director, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland. He will lecture on Prenatal Factors in Oral Pathologic Conditions.

This will be an open meeting to which members of the dental, medical and allied professions are cordially invited.

Michael Reese Hospital Medical Center

The Department of Dentisty will present The Loyola University School of Dentistry's Department of Periodontology in a two-week course in "Theory and Practice of Periodontics," Sept. 16 to 27, 1958.

The course will be under the direction of Dr. Balint Orban. He will be assisted by Drs. Harry Sicher, Frank Wentz, and John Kollar, all of Loyola University, and Joseph P. Weinman of the University of Illinois College of Dentistry.

The class will participate in examining patients, making diagnoses and prognoses, and planning treatment. It will perform root planing, surgery, and postoperative treatments.

The class will be limited to a small number. Applications will be accepted in the order received. The fee for the course is $400.00. Full details and complete program can be obtained by writing to Dental Department, Michael Reese Hospital, 29th St. and Ellis Ave., Chicago 16, Illinois.

Rowe Smith Memorial Foundation

The Foundation announces its 1958-1959 annual seminar, to be held Jan. 18 to 21, 1959, at Fly-n-Fish Lodge on Caddo Lake, Karnack, Texas.

The subject will be "The Blood and Bleeding." The following clinicians will participate: E. Cheraskin, M.D., D.M.D., Chairman of the Department of Oral Medicine, University of Alabama School of Dentistry; Joseph M. Hill, M.D., Director, Wadley Research Institute and Blood Bank, Dallas, Texas; Raymond W. Monto, M.D., Physician-in-Charge, Division of Hematology, Henry Ford Hospital, Detroit, Michigan; and Robert B. Shira, D.D.S., Chief of Oral Surgery, Walter Reed Army Hospital, Washington, D. C. Dr. Lon Morrey, Editor of the *Journal of the American Dental Association*, will be guest of honor.

A brochure describing the program can be procured through the Rowe Smith Memorial Foundation, 501 State National Bank Bldg., Texarkana, Arkansas.

University of Alabama

On Sept. 20, 21, and 22, 1958, William T. Heron will present a course in "Hypnosis Applied to Dentistry." Dr. Heron is Professor of Psychology at the University of Minnesota, Minneapolis, Minnesota, and author of the text entitled *Clinical Applications of Suggestion and Hypnosis.* The tuition fee is $100.00, and the class will be limited.

For further information please write to the Director, Refresher Course Program, University of Alabama School of Dentistry, 1919 Seventh Avenue South, Birmingham, Alabama.

REVIEWS OF NEW BOOKS

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Practical Otolaryngology. By Gervais Ward McAuliffe, M.D., F.A.C.S., F.I.C.S., Associate Clinical Professor of Otolaryngology, Cornell University Medical College; Attending Otolaryngologist, New York Hospital; Diplomate, American Board of Otolaryngology, American Trilogical Society, American Board of Plastic Surgery, Harvey Society, Pan-Pacific Surgical Association. New York, The Blakiston Division of The McGraw-Hill Book Co., Inc. Price, $7.00.

According to its author, this book is written for the general practitioner of medicine with the hope of providing a reference for the more common problems in otolaryngology. It is a short book and easily readable. Many tables and step-by-step descriptions of certain procedures are included. Its index is quite adequate.

Many inaccuracies are present, however, and the detailing of obsolete methods of treatment could better have been eliminated. One of the most common problems encountered in general practice is the treatment of external otitis. Less than one page is devoted to this, while an entire chapter of seven and one-half pages is devoted to "The Wet Suction Irrigation Technique in the Treatment of Infection of the Tonsil."

Perhaps the chief value of this book is the description of certain procedures which have been developed by the author and used by him satisfactorily for many years in the examination and treatment of patients. Illustrative case reports are interspersed throughout the text. One four-page chapter is devoted to "Maxims in Otolaryngology," which capsules the author's rich experience by means of well-chosen aphorisms.

J. R. CHANDLER

Injuries of the Bones of the Head (An Atlas of Clinical and X-ray Diagnosis). By J. Vondra and R. Bláha. Artia, Prague, Czechoslovakia. 304 pages. 170 illustrations, including sixteen color plates.

Injuries of the Bones of the Head is a translation from a Czechoslovakian volume. The authors have attempted to present the signs of head injuries requiring first aid. The book was designed primarily for general practitioners in busy health centers who are in need of information regarding primary first-aid treatment of head injuries.

The book is divided into the following four parts, with descriptive text and x-rays:

1. Fractures of the Vault of the Skull
2. Fractures of the Base of the Skull
3. Fractures of the Bones of the Face
4. Injuries of the Mandible and Mandibular Joint

E. L. S.

ABSTRACTS OF CURRENT LITERATURE

CLINICAL AND LABORATORY RESEARCH

Studies on the Acid Decalcification of Human Dental Enamel. Joan E. Hills, M.Sc. (Sydney), and H. R. Sullivan, D.D.Sc. (Sydney), Institute of Dental Research, United Dental Hospital, Sydney. Australian Dent. J. 3: 6-18, February, 1958.

The solubility of powdered dental enamel was studied in a series of citrate and lactate buffers with various pH values containing various amounts of calcium phosphate (hydroxyapatite). The effect of the presence of carbon dioxide on the solution of the enamel was also investigated.

From the results of these investigations, it was concluded that the constituents of the enamel dissolve in the proportions in which they occur in the solid phase and that the pH value at which this solution occurs depends upon the concentration of calcium and phosphorus present in the environment. There was no preferential solution of the carbonate from the enamel; nor did the presence of carbon dioxide in the system have any effect on the solution of the enamel.

A. J. A.

Dental Observations on Australian Aborigines—Continuously Changing Functional Occlusion. M. J. Barrett, M.D.S., Dental School, University of Adelaide. Australian Dent. J. 3: 39-52, February, 1958.

This article reports a study on the teeth and dental arches of full-blooded Australian aborigines living at Yuendumu Native Settlement in Central Australia. It deals in some detail with the significance of the well-known marked wear of aboriginal teeth.

Attrition commences at an early age, is progressive throughout life, and develops a more or less characteristic pattern. The pattern of wear is one of continued change which affects not only the shape of the teeth but also the manner of occlusion of the dental arches.

The pattern of wear established in the deciduous dentition determines, to some extent at least, the developing pattern of wear in the permanent dentition.

The meaning of the term "occlusion" is discussed. As seen in these aboriginal subjects, occlusion is a functional relationship of the teeth—a dynamic process which undergoes continual change throughout the dental life of the individual. At no stage does the aboriginal occlusion resemble the so-called ideal occlusion of unworn teeth of civilized man.

Centric occlusion, as generally understood or implied, does not exist in the well-worn dental arches of many of the adult natives examined at Yuendumu.

A. J. A.